B7

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 930 298 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
18.12.2002 Bulletin 2002/51

(21) Application number: **97933037.0**

(22) Date of filing: **28.07.1997**

(51) Int Cl.[7]: **C07D 211/46**, C07D 211/58, C07D 213/75, C07D 401/06, C07D 405/06, C07D 409/06, A61K 31/445, C07C 59/56

(86) International application number:
PCT/JP97/02600

(87) International publication number:
WO 98/005641 (12.02.1998 Gazette 1998/06)

(54) FLUORINATED 1,4-DISUBSTITUTED PIPERIDINE DERIVATIVES

FLUORIERTE 1,4-DISUBSTITUIERTE PIPERIDIN-DERIVATE

DERIVES DE PIPERIDINE FLUORES A DISUBSTITUTION EN POSITION 1,4

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
LT LV RO SI

(30) Priority: **01.08.1996 JP 21943696**
21.02.1997 JP 5397997

(43) Date of publication of application:
21.07.1999 Bulletin 1999/29

(73) Proprietor: **BANYU PHARMACEUTICAL CO., LTD.**
Chuo-ku, Tokyo 103-8416 (JP)

(72) Inventors:
- **TSUCHIYA, Yoshimi,Banyu Pharmaceutical Co., Ltd.**
  Ibaaraki 300-2611 (JP)
- **NOMOTO, Takashi,Banyu Pharmaceutical Co., Ltd.**
  Menuma-machi, Osato-gun,Saitama 360-0214 (JP)
- **OHSAWA, Hirokazu.Banyu Pharmaceutical Co., Ltd.**
  Ibaraki 300-2611 (JP)
- **KAWAKAMI, Kumiko.,Banyu Pharmaceutical Co., Ltd.**
  Ibaraki 300-2611 (JP)
- **OHWAKI, Kenji.,Banyu Pharmaceutical Co., Ltd.**
  Ibaraki 300-2611 (JP)
- **NISHIKIBE, Masaru.,Banyu Pharmaceutical Co., Ltd.**
  Iaraki 300-2611 (JP)

(74) Representative:
Weisert, Annekäte, Dipl.-Ing. Dr.-Ing.
Patentanwälte
Kraus & Weisert
Thomas-Wimmer-Ring 15
80539 München (DE)

(56) References cited:
EP-A- 0 751 127
EP-A- 0 863 141
WO-A-96/33973
WO-A-97/13766
GB-A- 2 249 093

- **DATABASE WPI Section Ch, Week 199515 Derwent Publications Ltd., London, GB; Class B02, AN 1995-115385 XP002133604 -& WO 95 06635 A (YAMANOUCHI PHARM CO LTD) , 9 March 1995 (1995-03-09)**
- **MAREK K L ET AL: "STIMULATION OF ACETYLCHOLINE SYNTHESIS BY BLOCKADE OF PRESYNAPTIC MUSCARINIC INHIBITION AUTORECEPTORS: OBSERVATIONS IN TAT AND HUMAN BRAIN PREPARATIONS AND COMPARISON WITH THE EFFECT OF CHOLINE" LIFE SCIENCES, vol. 30, no. 18, 1 January 1982 (1982-01-01), pages 1517-1524, XP002067290 ISSN: 0024-3205**
- **JOURNAL OF MEDICINAL CHEMISTRY, 1989, Vol. 32, No. 10, TEMPLE CARROLL Jr. et al., "New Anticancer Agents", p. 2364.**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 930 298 B1

Description

Technical Field

[0001] This invention relates to novel fluorine-containing 1,4-disubstituted piperidine derivatives, processes for preparing them, pharmaceutics containing them and their use as medicines, especially in the treatment or prophylaxis of various diseases of the respiratory, urinary and digestive systems.

Background Art

[0002] Antagonism to muscarinic receptors are known to cause bronchodilation, gastrointestinal hypanakinesis, gastric hyposecretion, dry mouth, mydriasis, suppression of bladder contraction, hypohidrosis, tachycardia and the like ["Basic and Clinical Pharmacology", 4th ed., APPLETON & LANGE, pp. 83-92 (1989); Drug News & Perspective, 5(6), pp. 345-352 (1992)].

[0003] It has been made clear that there are at least three subtypes of muscarinic receptors; the M_1 receptors being present mainly in the brain, the M_2 receptors mainly in the heart, and the M_3 receptors, on smooth muscles and glandular tissues. Whereas, all of the large number of compounds heretofore known to exhibit antagonism to muscarinic receptors non-selectively antagonize the three subtypes of muscarinic receptors. Consequently, attempts to use these compounds as therapeutic or prophylactic agents for diseases of the respiratory system have caused undesirable side effects such as dry mouth, nausea and mydriasis. Still in addition, particularly serious side effects associated with the central nervous system, such as dementia, attributable to the M_1 receptors and those associated with the heart, such as tachycardia mediated by the M_2 receptors pose problems and their solution is strongly demanded.

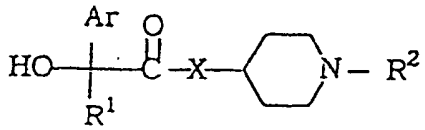
[0004] We have disclosed, as a drug meeting the demand, 1,4-disubstituted piperidine derivatives (see: PCT WO96/33973). However, creation of even more excellent drug has been in demand.

[0005] An object of the present invention is to create even a better drug than said known compounds, whereby to provide pharmaceutics exhibiting highly selective antagonism to M_3 receptors and minimizing adverse side effect and which, therefore, provide safe and effective pharmaceutics for treatment or prophylaxis of diseases associated with muscarine M_3 receptors, eg., such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis; digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system; urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystisis; and motion sickness.

[0006] WO 95/06635 (Database WPI Section Ch, week 199515, Derwent Publications Ltd., London, GB AN: 1995-115385), GB-A 2 249 093 and EP-A-0 863 141 (Article 54(3) EPC document) disclose 1,4-disubstituted piperidine derivatives having selective M_3 muscarinic receptor antagonist activity.

Disclosure of the Invention

[0007] According to the present invention, there are provided novel fluorine-containing 1,4-disubstituted piperidine derivatives of the general formula [I]



[I]

and pharmaceutically acceptable salts thereof, wherein:

Ar represents a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, amino and C_1-C_6 alkylamino;

R^1 is 3,3-difluorocyclopentyl; R^2 is 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyridylmethyl or benzyl (any 1-3 hydrogen atoms on the ring in the thienylmethyl, furylmethyl, pyridylmethyl or benzyl group may be substituted with C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, amino or C_1-C_6 alkylamino);

and

X stands for 0 or NH.

[0008] The compounds of the above formula [I] which are provided by the present invention have potent and selective antagonistic activity for muscarinic M_3 receptors, and exhibit excellent oral activity, duration of action and pharmacokinetics, so that they have little side effects and are safe. Hence, they are very useful in the treatment or prophylaxis of diseases such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system: urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystisis: and motion sickness.

[0009] Hereinafter the meaning of the technical terms used in the present specification are elucidated and the invention is explained in further details.

[0010] "Halogen" include fluorine, chlorine, bromine 35 and iodine.

[0011] "Lower alkyl" signifies C_1-C_6 straight chain or branched alkyl groups, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl, isopentyl, hexyl and isohexyl groups.

[0012] "Lower alkoxy" signifies C_1-C_6 straight chain or branched alkoxy groups, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, isobutoxy, t-butoxy, pentyloxy, isopentyloxy, hexyloxy and isohexyloxy groups.

[0013] "Lower alkoxycarbonyl" signifies C_1-C_7 straight chain or branched alkoxycarbonyl groups, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, sec-butoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, hexyloxycarbonyl and isohexyloxycarbonyl groups.

[0014] "Aralkyloxycarbonyl" signifies C_7-C_{10} aralkyloxycarbonyl groups, for example, benzyloxycarbonyl and phenethyloxycarbonyl groups.

[0015] "Lower alkylamino" signifies C_1-C_6 straight chain or branched alkylamino groups, for example, methylamino, ethylamino, propylamino, isopropylamino, butylamino, sec-butylamino, t-butylamino, pentylamino, isopentylamino, hexylamino, isohexylamino, dimethylamino, diethylamino and dipropylamino groups.

[0016] "Protected hydroxyl groups" signify hydroxyl groups which are protected with acyl such as acetyl, alkylsilyl such as trimethylsilyl and t-butyldimethylsilyl, aralkyl such as benzyl and trityl, ether group such as methoxymethyl, and in the form of alkylideneketal such as isopropylideneketal.

[0017] "Protected oxo groups" signify oxo groups which are protected in the form of acetal or ketal such as ethylene ketal, trimethylene ketal and dimethyl ketal.

[0018] "Protected amino or lower alkylamino groups" signify amino or lower alkylamino groups which are protected with, for example, aralkyl groups such as benzyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl and trityl; lower alkanoyl groups such as formyl, acetyl and propionyl; arylalkanoyl groups such as phenylacetyl and phenoxyacetyl; lower alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, isobutoxycarbonyl and t-butoxycarbonyl; alkenyloxycarbonyl groups such as 2-propenyloxycarbonyl; aralkyloxycarbonyl groups such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl, and lower alkylsilyl groups such as trimethylsilyl and t-butyldimethylsilyl. In particular, amino or lower alkylamino groups which are protected with t-butoxycarbonyl and benzyloxycarbonyl groups are preferred.

[0019] Also "deprotection" signifies removal of protective groups by the means conventionally used in the field of organic chemistry, such as hydrolysis, hydrogenolysis and the like.

[0020] Referring to the general formula [I],

(1) Ar represents a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, amino and C_1-C_6 alkylamino;

(2) R^1 is 3,3-difluorocyclopentyl.

(3) X represents 0 or NH, NH being the preferred.

(4) R^2 represents 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyridylmethyl or benzyl (any 1-3 hydrogen atoms on the ring in the thienylmethyl, furylmethyl, pyridylmethyl or benzyl group may be substituted with lower alkyl, trifluoromethyl, cyano, hydroxyl, nitro, lower alkoxycarbonyl, halogen, amino, lower alkylamino or lower alkoxy).

[0021] The 6-aminopyridin-2-ylmethyl group is preferred.

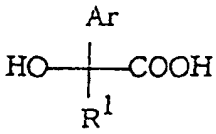
[0022] According to the manner of substitution, the compounds of the present invention may exist in the form of stereoisomers such as optical isomers, diastereoisomers and geometrical isomers. It is to be understood that the

compounds of the present invention also include all such stereoisomers and mixtures thereof.

[0023] Moreover, the compounds of the present invention may exist in the form of pharmaceutically acceptable salts. Such salts include inorganic acid salts such as hydrochlorides, sulfates, nitrates, phosphates and perchlorates; organic carboxylic acid salts such as maleates, fumarates, succinates, tartrates, citrates and ascorbates; organic sulfonic acid salts such as methanesulfonates, isethionates, benzenesulfonates and p-toluenesulfonates; and the like.

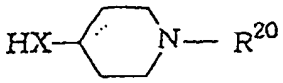
[0024] The compounds of the above general formula [I] in accordance with the present invention can be prepared, for example, by:

(a) reacting a carboxylic acid of the general formula [III]



[III]

[wherein Ar and R^1 have the same signification as defined above]
or a reactive derivative thereof with a compound of the general formula [IV]



[IV]

[wherein R^{20} represents benzyl, 2-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl or 3-furylmethyl,

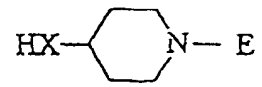
(any 1 to 3 hydrogen atoms on the ring may be substituted with C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, unprotected or protected amino, unprotected or protected C_1-C_6 alkylamino or aralkyloxycarbonyl;

protected amino or C_1-C_6 alkylamino group signifies amino or C_1-C_6 alkylamino group which is protected with benzyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl, trityl ; formyl, acetyl, propionyl, phenylacetyl, phenoxyacetyl, methoxycarbonyl, ethoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, 2-propenyloxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, trimethylsilyl and t-butyldimethylsilyl; and X stands for NH or O] or a salt thereof;

and when

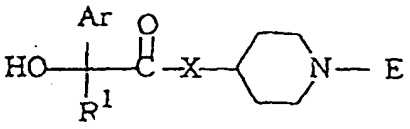
R^{20} has protected amino or protected C_1-C_6 alkylamino group(s), removing the protective group(s); and when R^{20} has C_1-C_7 alkoxycarbonyl or C_7-C_{10} aralkyloxycarbonyl, converting the same to amino; or

(b) reacting a carboxylic acid of the above general formula [III] or a reactive derivative thereof with a compound of the general formula [V]



[V]

[wherein E is a protective group for the imino group, which signifies similar protective groups to those for amino as above, and X is as defined above]
or a salt thereof; deprotecting the resulting compound of the general formula [VI]



[VI]

[wherein Ar, R^1, X and E are as defined above] thereafter reacting the same with a compound of the general formula [VII]

$$R^{20}\text{-}L \qquad [VII]$$

[wherein L represents halogen atoms such as chlorine, bromine and iodine; methanesulfonyloxy; or p-toluenesulfonyloxy and R^{20} is as defined above] in the presence of a base, if necessary, and again if necessary conducting a conversion reaction of R^{20} similar to the above; or

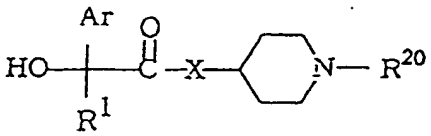
(c) deprotecting a compound of the above general formula [VI] and subjecting it to a reductive alkylation reaction with a compound of the general formula [VIII]

$$R^{21}\text{-}CHO \qquad [VIII]$$

[wherein R^{21} represents phenyl, 2-pyridyl, 2-thienyl, 3-thienyl, 2-furyl or 3-furyl (any 1 to 3 hydrogen atoms on the ring may be substituted with C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, unprotected or protected amino, unprotected or protected C_1-C_6 alkylamino or aralkyloxycarbonyl); and protected amino and protected C_1-C_6 alkyl amine are as defined above],

and if necessary conducting the conversion reaction of R^{21} similar to the foregoing.

[0025] In the above-described process variant (a), a carboxylic acid of formula [III] is reacted with a compound of formula [IV] or a salt thereof in the presence of a suitable condensing agent. Thus, there is obtained a coupled compound of the general formula [IX]



[IX]

[wherein Ar, R^1 , X and R^{20} are as defined above].

[0026] The carboxylic acid of formula [III] used as a starting material in the above condensation reaction can be prepared, for example, by the method as described in Referential Examples.

[0027] The condensing agent to be used in the above-described reaction may be any of those which are commonly used in the field of organic synthetic chemistry for condensation reactions of carboxyl groups with hydroxyl or amino groups, and examples thereof include N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diphenylphosphoryl azide and dipyridyl disulfide-triphenylphosphine. Of these, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide is preferred.

[0028] Use rate of these condensing agents are subject to no critical limitation, while normally it may be within a range of 1 to 5 equivalents, preferably 1 to 2 equivalents, per mole of the compound of formula [III].

[0029] If necessary, the above-described condensation reaction may be carried out in the presence of a base. Bases which can be used for this purpose include, for example, aliphatic tertiary amines such as triethylamine and diisopropylethylamine; and aromatic amines such as pyridine, 4-dimethylaminopyridine, quinoline. 4-Dimethylaminopyridine is particularly preferred.

[0030] The condensation reaction is preferably carried out in an inert solvent. Suitable inert organic solvents include, for example, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene and mixtures of the foregoing solvents. Of these, diethyl ether, tetrahydrofuran, N,N-dimethylformamide and dioxane are preferred.

[0031] The reaction temperature may usually range from -70°C to the boiling point of the solvent used for the reaction and preferably from -20°C to 100°C. Under these conditions, the reaction can usually be completed in a period of time ranging from 5 minutes to 7 days and preferably from 10 minutes to 24 hours.

[0032] The proportion of the compound of formula [IV] or a salt thereof to the compound of formula [III] is not critical and may vary according to the kinds of individual compounds, the reaction conditions employed and other factors. Whereas, the compound of formula [IV] or a salt thereof may usually be used in an amount of 1 to 5 moles, preferably

1 to 2 moles, per mole of the compound of formula [III].

[0033] The coupled compound of the above formula [IX] can also be obtained by converting the carboxylic acid of formula [III] into a reactive derivative thereof and condensing it with the compound of formula [IV] or a salt thereof.

[0034] Suitable reactive derivatives of the carboxylic acid of formula [III] include, for example, compounds which are commonly used in the field of organic synthetic chemistry for activation of carboxyl group(s) in an esterification or amidation reaction, such as mixed acid anhydrides, active esters and active amides.

[0035] Mixed acid anhydrides of the carboxylic acid of formula [III] can be obtained by reacting the carboxylic acid of formula [III] with an alkyl chlorocarbonate, e.g., ethyl chlorocarbonate, an aliphatic carboxylic acid chloride, e.g., acetyl chloride, pivaloyl chloride or the like according to conventional method. Reactive esters thereof can be obtained by reacting the carboxylic acid of formula [III] with an N-hydroxy compound, e.g., N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxybenzotriazole; or a phenol compound, e.g., 4-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol, pentachlorophenol or the like; in the presence of a condensing agent, e.g., N,N'-dicyclohexylcarbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, diphenylphosphoryl azide or dipyridyl disulfide-triphenylphosphine, according to conventional method. Reactive amides thereof can be obtained by reacting the carboxylic acid of formula [III] with 1,1'-carbonyldiimidazole, 1,1'-carbonylbis(2-methylimidazole) or the like according to conventional method.

[0036] The condensation reaction of a reactive derivative of a carboxylic acid of formula [III] with a compound of formula [IV] or a salt thereof is preferably carried out in an inert solvent. Suitable inert organic solvents include, for example, diethyl ether, tetrahydrofuran, N,N-dimethylformamide, dioxane, benzene, toluene, chlorobenzene, methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethylene and mixtures of the foregoing solvents. Of these, diethyl ether, chloroform, tetrahydrofuran, N,N-dimethylformamide and dioxane are preferred.

[0037] The reaction temperature may usually range from -70°C to the boiling point of the solvent used for the reaction and preferably from -20°C to 100°C.

[0038] The proportion of the compound of formula [IV] or a salt thereof to the reactive derivative of a carboxylic acid of formula [III] is not critical and may vary according to the kind of the reactive derivative and other factors, while the compound of formula [IV] or a salt thereof may usually be used in an amount of 1 to 5 moles, preferably 1 to 2 moles, per mole of the reactive derivative of the carboxylic acid of formula [III].

[0039] When R^{20} in the compounds expressed by general formula [IV] or [IX] has protected amino group(s) or protected lower alkylamino group(s), the protective group(s) are removed if necessary; when lower alkoxycarbonyl or aryloxycarbonyl group(s) are present, the functional group(s) are suitably converted to amino group(s). Removal of amino-protective groups can be effected by processes known per se, for example, any of those described in Protective Groups in Organic Synthesis, T.W. Greene, John Wiley & Sons Co. (1981) or methods analogous thereto, for example, solvolysis using an acid or base, chemical reduction using a metal hydride complex or the like and catalytic reduction using palladium-on-carbon, Raney-nickel or the like.

[0040] Solvolysis with an acid can normally be carried out by treating the compound with an acid such as formic acid, trifluoroacetic acid, hydrochloric acid or sulfuric acid, in an inert solvent such as methylene chloride, anisole, tetrahydrofuran, dioxane, methanol or ethanol or a mixture of such a solvent and water, or in the absence of solvent, preferably at a temperature in the range from about 0° to about 100°C, for a period of time ranging from 10 minutes to 24 hours.

[0041] Solvolysis with a base can normally be carried out by treating the compound with an alkali metal hydroxide, e.g., lithium hydroxide, sodium hydroxide or potassium hydroxide; an alkali metal carbonate, e.g., sodium carbonate or potassium carbonate, in an inert solvent which exerts no adverse effect on the reaction, e.g., methanol, ethanol, isopropanol, tetrahydrofuran or dioxane or a mixture of such a solvent and water, preferably at a temperature in the range of from about -20 to about 80°C, for a period of time ranging from 10 minutes to 24 hours.

[0042] Catalytic reduction can normally be carried out in the presence of a catalyst such as palladium-on-carbon, palladium hydroxide, Raney nickel or platinum oxide, in an inert solvent, e.g., methanol, ethanol, water or acetic acid or a mixture of such solvents, preferably under a pressure of hydrogen of about 1 to about 20 kg/cm^2, preferably at a temperature in the range of from about 0 to about 40°C, for a period of time ranging from 10 minutes to 24 hours.

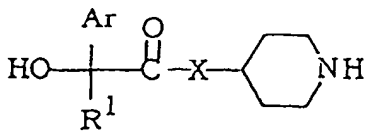
[0043] Conversion of the lower alkoxycarbonyl or aralkyloxycarbonyl to amino can be conducted by either reacting the compound with hydrazine to form an acid hydrazide and thereafter converting it to the corresponding acid azide; or converting the compound to a carboxylic acid by hydrolysis, then to an acid azide, followed by rearrangement and hydrolysis.

[0044] In the process variant (b), the condensation reaction of a carboxylic acid of formula [III] or a reactive derivative thereof with a piperidine derivative of formula [V] in the first stage can be practiced in the manner similar to the condensation reaction of a carboxylic acid of formula [III] or a reactive derivative thereof with a compound of formula [IV] in the process variant (a).

[0045] The compound of the foregoing formula [VI] obtained through this condensation reaction is then removed of the protective group(s) of imino group(s).

[0046] Removal of said imino-protective groups from a compound of formula [VI] can be effected in the manner similar to above-described removal of amino-protective groups.

[0047] Thus obtained compounds of the general formula [X]



[X]

[wherein Ar, R^1 and X are as defined above] is reacted with a compound of formula [VII] in the second stage, if necessary in the presence of a base.

[0048] The reaction of the compound of formula [X] with the compound of formula [VII] is usually carried out in a suitable solvent by using the compounds in substantially equimolar amounts or using either of the compounds in slight excess (e.g., using the compound of formula [VII] in an amount of 1 to 1.3 moles per mole of the compound of formula [X]). If desired, however, either of the compounds may be used in large excess. Moreover, a suitable base and/or an additive may be used.

[0049] Suitable solvents include, for example, ethers such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene, toluene, chlorobenzene and xylene; aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, acetonitrile and hexamethylphosphoric triamide; and mixtures thereof.

[0050] Bases which can be used for above-described reaction include, for example, alkali metal bicarbonates such as sodium hydrogen carbonate and potassium hydrogen carbonate; alkali metal carbonates such as sodium carbonate and potassium carbonate; tertiary aliphatic amines such as trimethylamine, triethylamine, N,N-diisopropylethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN); and aromatic amines such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline and isoquinoline. Of these, N,N-diisopropylethylamine and potassium carbonate are preferred.

[0051] Additives which can be used for above-described reaction include, for example, alkali metal iodides such as lithium iodide, sodium iodide and potassium iodide. Of these, potassium iodide is preferred.

[0052] The reaction temperature may usually range from about 0°C to the boiling point of the solvent, and the reaction time may usually range from 10 minutes to 48 hours. If desired, however, reaction conditions beyond these limits may be used.

[0053] If necessary, furthermore, conversion reactions of R^{20} as described as to the process variant (a) are conducted.

[0054] The reductive alkylation reaction of a compound of the above formula [X] with an aldehyde of formula [VIII] according to the process variant (c) is normally carried out in an inert solvent which exerts no adverse effect on the reaction. Suitable inert solvents include, for example, alcohols such as methanol and ethanol; ethers such as diethyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons such as benzene and toluene; and mixtures thereof. Of these, methanol, ethanol, tetrahydrofuran and toluene are preferred.

[0055] The reaction temperature may usually range from about -30°C to about 200°C and preferably from about 0°C to about 100°C. The reaction time may usually range from 10 minutes to 7 days and preferably from 10 minutes to 24 hours.

[0056] The above-described reductive alkylation reaction is preferably carried out under weakly acidic conditions which facilitate formation of Schiff bases. Acids which can be used for the necessary pH control include, for example, p-toluenesulfonic acid, hydrochloric acid, acetic acid and trifluoroacetic acid.

[0057] The reductive alkylation can be effected, for example, using a metal hydride complex such as sodium borohydride, sodium cyanoborohydride, lithium aluminum hydride or sodium triacetoxyborohydride, or by catalytic reduction using a palladium-on-carbon catalyst, a Raney nickel catalyst or the like. Preferably, it is effected using a metal hydride complex such as sodium borohydride or sodium cyanoborohydride. Especially when the reductive alkylation is carried out under weakly acidic conditions which facilitate formation of Schiff bases, it is preferable to use sodium cyanoborohydride or the like which are relatively stable in the acidic pH range.

[0058] When a metal hydride complex is used as the reducing agent, the amount of reducing agent used may usually range from 1 mole to excessive moles, preferably from 1 to 10 moles, per mole of the compound of formula [X].

[0059] If necessary, then the conversion reactions of R^{21} as described as to the process variant (a) are carried out.

[0060] The compounds of formula [I] which are obtained according to the above-described process variants (a), (b) and (c) can be isolated and purified by those methods known per se, i.e. such customarily used separation means as column chromatography using silica gel, adsorbent resin or the like, liquid chromatography, thin-layer chromatography; solvent extraction or recrystallization and reprecipitation.

[0061] The compounds of the present invention and intermediates thereof exist in stereoisomeric forms such as

enantiomeric isomers, diastereoisomers and geometrical isomers. It is to be understood that the compounds of the present invention also include all such stereoisomerically pure substances and mixtures thereof. When the compounds of the present invention and intermediates thereof are racemates, their optical resolution can be achieved by conventional means such as high-performance liquid chromatography using a chiral carrier or fractional crystallization of a diastereomeric salt.

[0062] The compounds of formula [I] obtained in the above-described manner may be converted into pharmaceutically acceptable salts thereof according to usual manner. Conversely, such salts may also be converted into the corresponding free amines according to usual manner.

[0063] The compounds of formula [I] in accordance with the present invention exhibit potent and selective inhibitory activity for binding to muscarinic receptors, a potent and selective antagonism to muscarinic receptors in vitro and, furthermore, potent and durable bronchodilatory action in vivo. These activities exhibited by the compounds of the present invention are demonstrated by the following tests on the inhibition of binding to muscarinic receptors and tests on antagonism against various muscarinic receptors.

Tests on inhibition of binding to muscarinic receptors

[0064] These tests were performed according to a modification of the method of Hargreaves et al. (Br. J. Pharmacol. 107: 494-501, 1992). Muscarinic receptors m1, m2 and m3 expressed in CHO cells (Receptor Biology, Inc.) were incubated with 0.2 nM [^{3}H]-N-methylscopolamine (84Ci/mmol, New England Nuclear, Inc.) and a test compound to be tested in 0.5 ml of 50 mM Tris-HCl - 10 mM $MgCl_2$ - 1 mM EDTA (pH 7.4) for 120 minutes at room temperature (about 20-25°C), followed by suction filtration over glass filters (UniFilter-GF/C; Packard). Then the filter was washed four times with 1 ml of ice-cold Tris-HCl buffer and dried at 50°C for an hour. After adding a scintillator (Microscinti 0; Packard), the radioactivity of [^{3}H]-N[^{3}H]-N-methylscopolamine binding to the filter was counted by a microplate scintillation counter (TopCount™; Packard). Non-specific binding of [^{3}H]-N-methylscopolamine was measured by adding 1 μM N-methylscopolamine. According to the method of Cheng and Prussoff (Biochem. Pharmacol. 22: 3099-3108, 1973), the binding affinity (Ki value) of a compound of the present invention for muscarinic receptors was calculated from the concentration of the test compound which achieved 50% inhibition of binding of [^{3}H]-N-methylscopolamine, labeled ligand (IC_{50} value).

Table 1

Inhibitory Effects on Binding to Muscarinic m_2 and m_3 Receptors			
	Ki (nM)		m_2/m_3
	m_2	m_3	
Compound of Example 1*	3200	5.5	590
Compound of Example 10	17000	8.9	1900
Compound of Example 11	460	3.2	140
Compound of Example 12	8600	30	290
Compound of Example 14	1400	10	140
Compound of Example 15	1000	3.5	290
Compound of Example 20	550	3.0	180
Compound of Example 21	50000	22	2300
Compound of Example 22	13000	19	680
Compound of Example 26	24000	22	1100
Compound of Example 27	4200	20	210
Compound of Example 31	10000	19	520

* Comparative

[0065] As is clear from the results indicated in above Table 1, those compounds of the present invention exhibited far higher binding-inhibitory activity to m_3 receptor, than to m_2 receptor.

Tests for Antagonism to Muscarinic Receptors (in vitro)

1) Tests for antagonism to M_2 receptor in an isolated rat right atrium

[0066] These tests were performed according to a conventional method. A male SD strain rat (weighing 300-500 g) was killed by exsanguination, and the right atrium was isolated. This preparation was isometrically suspended in organ bath filled with 20 ml of Krebs-Henseleit solution (gassed with 95% O_2 - 5% CO_2 and kept at 32°C) with an initial tension of 0.5 g. The heart rate was recorded with a heart rate counter. After the preparation was equilibrated for 30 minutes, carbachol (10^{-9} to 10^{-6} M) was cumulatively administered in three-fold increasing doses. Thus, a decrease in heart rate was measured to obtain a dose-response curve for the control experiment. After the preparation was washed with fresh solution to restore the heart rate, a test compound was administered thereto. Ten minutes later, carbachol was cumulatively administered again. Responses to carbachol were expressed as percentages based on the heart rate before administration of carbachol as 100%. The antagonistic potency (K_B value) of the test compound was determined from the degree of shift of the dose-response curve obtained by treatment with individual test compound of the present invention.

2) Tests for antagonism to the airway M_3 receptor in an isolated rat trachea

[0067] These tests were performed according to a conventional method. A male SD strain rat (weighing 300-500 g) was killed by exsanguination, and the trachea was isolated. Annular segments (2 mm wide) were cut out from the trachea and cut transversely at the anterior cartilage part to make open ring preparation. A preparation was suspended in a Magnus tube filled with 5 ml of Krebs-Henseleit solution (gassed with 95% O_2 - 5% CO_2 and kept at 32°C) with an initial tension of 1.0 g and a resting tension of 0.6 g. The tension of the preparation was recorded isometrically. After being equilibrated for an hour, the preparation was made to contract twice by treatment with 10^{-4} M carbachol, and the second contraction induced by carbachol was used as the reference contraction. After the preparation was washed with fresh solution to be restored to the base line, a test compound was administered thereto (or no treatment was given). Ten minutes later, carbachol (10^{-8} to 10^{-3} M) was cumulatively administered in three-fold increasing doses to obtain a dose-response curve. The dose-response curve was plotted by expressing responses as percentages based on the reference contraction of the preparation as 100%. The antagonistic potency (K_B value) of the test compound was determined from the degree of shift of the dose-response curve obtained by treatment with the test compound.

TABLE 2

Antagonism to Muscarinic Receptors (in vitro)			
	K_B (nM)		M_2/M_3
	right atrium M_2	Trachea M_3	
Compound of Example 1*	1000	6.3	160
Compound of Example 11	610	0.95	640
Compound of Example 20	2100	1.6	630

* Comparative

[0068] As is clear from the results indicated in above Table 2, the compounds of the present invention exhibited far more powerful antagonism to the trachea M_3 receptor than to the right atrium M_2 receptor. Therefore, the compounds of the present invention are more selective for trachea M_3 receptor.

Tests for antagonism against muscarinic M_3 receptor (in vivo)

1-A) Tests for bronchodilation in rats (i.v.)

[0069] Eight- to eleven-weeks-old male rats of the Sprague-Dawley strain, weighing 380-420 g, were anesthetized with urethane (750 mg/kg, i.p.) and α-chloralose (37.5 mg/kg, i.p.). The bronchus of each rat was intubated, and the right jugular vein was cannulated for drug administration. After spontaneous respiration was fully suppressed by succinylcholine (5 mg/body, s.c.), the airway resistance was measured under artificial ventilation by means of a Pulmonary Mechanics Model 6 (Buxco). The acetylcholine (50 μg/kg, i.v.)-induced airway resistance increase was measured 5 minutes before and 5 minutes after administration of test compound, and the ratio of the airway resistance of the latter

to the former was calculated. In controls, isotonic sodium chloride solution was used in place of the test compounds and otherwise identical procedures were repeated, the calculated ratio of the airway resistance being set to be 100%. A dose that inhibited the acetylcholine-induced increase in airway resistance in the control groups by 50% was defined to be ED_{50}, and the ED_{50} values of the test compounds were calculated by probit analysis of their dose-response curves.

1-B) Tests for bronchodilation in rats (p.o.)

[0070] Eight- to eleven-weeks-old male rats of Sprague-Dawley strain weighing 380-420 g were orally administered with a test compound. The rats were treated in the identical manner as in the i.v. test, starting 30 minutes after the administration, and their airway resistance values were measured. The acetylcholine-(50 μg/kg, i.v.) induced airway resistance increase were measured 60 minutes after the administration of test compounds. In controls, isotonic sodium chloride solution was used in place of the test compounds and otherwise identical procedures were repeated, the airway resistance values being set to be 100%. A dose that inhibited the acetylcholine-induced increase in airway resistance in the control groups by 50% was defined to be ED_{50}, and the ED_{50} values of the test compounds were calculated by probit analysis of their dose-response curves.

TABLE 3

Antagonism to Muscarinic Receptor (in vivo)		
	Inhibition of Airway Contraction ED_{50} (mg/kg)	
	iv	po
Compound of Example 1*	0.033	-
Compound of Example 11	0.032	0.22
Compound of Example 20	0.040	0.37
Compound of Example 26	0.37	0.95
atoropine	0.0043	-
ipratropium	0.0015	-

* Comparative

2) Tests for bronchodilation in dogs (p.o.)

[0071] Twelve- to twenty-four-months-old male beagle dogs (weighing 10-15 kg) were anesthetized with pentobarbital (30 mg/kg, i.v.) and intubated in their bronchus. Their airway sensitivity (methacholine inhalation threshold value) were measured by means of the methacholine provocation test at least twice at two-weeks interval, and the dogs showing a reproducible methacholine reaction threshold values[1)] ware selected. To those dogs whose methacholine reaction threshold value had been confirmed, the test compounds were orally administered (1 mg/kg). Four hours after the administration, the methacholine provocation test was conducted, and then the methacholine reaction threshold value[2)] after administration of the test compound was obtained.

[0072] The bronchodilator activity of the test compound was determined following equation:

$$\text{shift value} = \frac{\text{methacholine reaction threshold value}^{2)} \text{ after drug administration}}{\text{methacholine reaction threshold value}^{1)} \text{ without drug administration}}$$

[0073] The methacholine provocation test was conducted using Astograph TCK-6100H Model (Chest). Methacholine chloride was used as bronchoconstritor, which was diluted with isotonic sodium chloride solution in 10-grade concentration levels starting from 40,000 μg/ml, as 20,000, 10,000, 5,000, 2,500, 1,250, 625, 312.5, 156 and 78 μg/ml. These methacholine aerosols were inhaled to the test animal each for 1 min, starting from the lowest concentration level, and respiration resistance was continuously recorded. The concentration level at which the respiration resistance reached twice the initial value was recorded as the methacholine threshold value.

TABLE 4

Bronchodilation Activity in Dogs (Oral Administration)	
	Methacholine Provocation Test (1 mg/kg, p. o.)
	shift value (after 4 hrs.)
Compound of Example 11	21
Compound of Example 20	>69
Compound of Example 26	>64

[0074] As clearly demonstrated in above Table 4, the compounds of the present invention exhibited powerful bronchodilation action and long duration of the action.

[0075] As above, the compounds of formula [I] of the present invention, which are characterized by introduction of fluorine atom(s) thereinto, exhibit potent and selective antagonistic activity against muscarinic M_3 receptors and exhibit excellent oral activity, duration of action and pharmacokinetics. Hence, they can be administered to patients orally or parenterally as safe pharmaceutics exhibiting little side effects, in the treatment or prophylaxis of diseases such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system: urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystisis: and motion sickness.

[0076] In practically using the compounds of the present invention for the treatment or prophylaxis of such diseases, they may be combined with pharmaceutically acceptable adjuvants in the usual manner to prepare pharmaceutical compositions suitable for administration. For this purpose, there can be used a variety of adjuvants which are commonly used in the field of pharmaceutics. Such adjuvants include, for example, gelatin, lactose, sucrose, titanium oxide, starch, crystalline cellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, corn starch, microcrystalline wax, white petrolatum, magnesium aluminate metasilicate, anhydrous calcium phosphate, citric acid, trisodium citrate, hydroxypropyl cellulose, sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxyethylene, hardened castor oil, polyvinyl pyrrolidone, magnesium stearate, light anhydrous silicic acid, talc, vegetable oil, benzyl alcohol, acacia, propylene glycol, polyalkylene glycol, cyclodextrin and hydroxypropylcyclodextrin.

[0077] The dosage forms of pharmaceutical compositions prepared by using these adjuvants include solid preparations such as tablets, capsules, granules, powders and suppositories; liquid preparations such as syrups, elixirs and injections; and the like. These preparations may be formulated according to conventional techniques well-known in the field of pharmaceutics. Liquid preparations may be in a form which is dissolved or suspended in water or other suitable medium prior to use. In particular, injections may be in the form of a solution or suspension in physiological saline solution or a glucose solution, or in powder form for reconstitution by dissolution or suspension in physiological saline or a glucose solution prior to use. If desired, such injections may contain buffer agents and/or preservatives.

[0078] As preparations for oral administration, such formulation forms, besides ordinary tablets, capsules, granules, powders and the like, aerosols or dry powders for inhalation, elixirs containing spices or coloring agents or suspensions may be employed.

[0079] In these pharmaceutical compositions, a compound in accordance with the present invention may be present at a ratio of from 1.0 to 100% by weight, preferably 1.0 to 60% by weight, based on the total weight of the composition. These pharmaceutical compositions may additionally contain other therapeutically effective compounds.

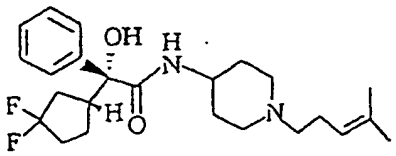
[0080] When the compounds of the present invention are used as drugs, their dosage level and dosage schedule may vary according to the sex, age and body weight of the patient, the severity of symptoms, the type and range of the desired therapeutic effect, and the like. Generally for oral administration, they are preferably administered in a daily dose of 0.1 to 100 mg/kg for adults and this daily dose may be given at a time or in several divided doses. For parenteral administration, they are preferably administered in a daily dose of 0.001 to 10 mg/kg for adults and this daily dose may be given at a time or in several divided doses.

[0081] Hereinafter the present invention is more specifically explained with reference to working examples, it being understood that the examples are in no way limitative of the scope of the invention.

Example 1 (comparative)

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0082] Structural formula



Step 1. Synthesis of 1 - (4-methyl-3-pentenyl) -4-piperidone

[0083] To a solution of 2.5 g of 4-piperidone monohydrochloride monohydrate in 150 ml of acetonitrile, 11 g of potassium carbonate, 2.62 g of 5-bromo-2-methyl-2-pentene and 800 mg of potassium iodide were added sequentially, and the mixture was heated under reflux for 3 hours. The reaction mixture was diluted with ethyl acetate, washed with water and then with brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 2.24 g of the title compound was obtained as a white solid.

Step 2. Synthesis of 4-amino-1-(4-methyl-3-pentenyl)-piperidine

[0084] To a solution of 2.2 g of 1-(4-methyl-3-pentenyl)-4-piperidone in 60 ml of methanol, 1.1 g of ammonium acetate and 860 mg of sodium cyanoborohydride were added sequentially, at room temperature, followed by stirring overnight at same temperature. Distilling the methanol off under reduced pressure, the pH of the reaction media was adjusted to 3 with 1N hydrochloric acid, followed by washing with diethyl ether. The aqueous layer was basified with 1N aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 1.9 g of the title compound was obtained as a colorless oil.

Step 3. Synthesis of (2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy - 2 -phenylacetamide

[0085] To a solution of 75 mg of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid in 3 ml of N,N-dimethylformamide, 55 mg of 1,1'-carbonyldiimidazole was added at room temperature, followed by stirring for 2 hours at the same temperature. Then 60 mg of 4-amino-1-(4-methyl-3-pentenyl)piperidine and 5 mg of 4-dimethylaminopyridine were added sequentially, followed by stirring overnight at room temperature. The reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate solution, water and brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified by preparative thin layer chromatography [Kieselgel™ $60F_{254}$, Art 5744 (Merck); chloroform / methanol = 10/1], to provide 23 mg of the title compound as an oil.

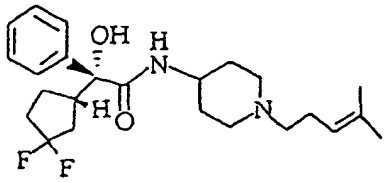
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.32-1.50 (2H, m), 1.60 (3H, s), 1.68 (3H, s) , 1.58-2.34 (12H, m) , 2.43-2.49 (1H, m) , 2.73-2.82 (3H, m) , 3.23-3.36 (1H, m), 3.48 (1H, brs), 3.62-3.73 (1H, m), 5.03-5.08 (1H, m), 6.29-6.33 (1H, m), 7.25-7.39 (3H, in), 7.54-7.57 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{34}F_2N_2O_2 + H)^+$) : 421.

Example 2 (comparative)

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0086] Structural formula



[0087] The title compound was prepared in the same manner as described in step 3 of Example 1 using (2R)-2-[(1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

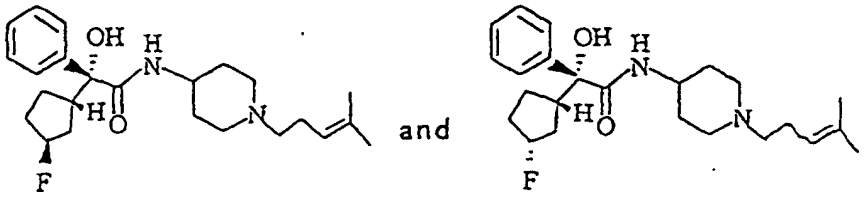
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.60 (3H, s), 1.68 (3H, s), 1.35-2.48 (15H, m), 2.75-2.86 (3H, m), 3.22-3.36 (1H, m), 3.48 (1H, brs), 3.61-3.76 (1H, m), 5.03-5.08 (1H, m), 6.27 (1H, d, J=8. 0Hz), 7.26-7.40 (3H, m), 7.55-7.58 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{34}F_2N_2O_2 + H)^+$) : 421.

Example 3 (comparative)

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1S,3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenyl]-acetamide and (2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-[(1S,3R)-3-fluorocyclopentyl]-2- hydroxy-2-phenylacetamide

[0088] Structural formulae



[0089] The title compounds were prepared using (2R)-2-[(1S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, in the same manner as described in step 3 in Example 1, and separated in the final step.

(2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-["(1S,3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0090] ^{1}H-NMR ($CDCl_3$, δ ppm) : 1.60 (3H, s), 1.68 (3H, s), 1.31-2.33 (15H, m), 2.44-2.49 (1H, m), 2.69-2.81 (2H, m), 3.19-3.30 (1H, m), 3.62-3.74 (1H, m), 3.90 (1H, brs), 5.03-5.28 (2H, m), 5.87-5.91 (1H, m), 7.25-7.40 (3H, m), 7.53-7.57 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{35}FN_2O_2 + H)^+$): 403

(2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-[(1S,3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

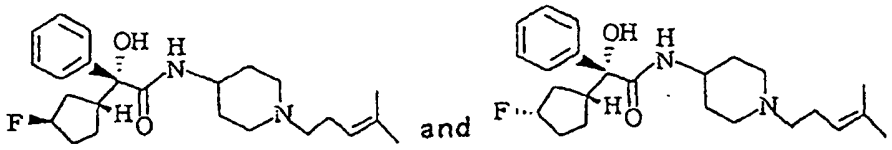
[0091] ^{1}H-NMR ($CDCl_3$, δ ppm) : 1.61 (3H, s), 1.68 (3H, s), 1.37-2.26 (14H, m), 2.32-2.37 (2H, m), 2.75-2.90 (2H, m), 3.43-3.56 (1H, m), 3.62-3.76 (1H, m), 5.04-5.13 (2H, m), 6.91-6.95 (1H, m), 7.23-7.35 (3H, m), 7.67-7.71 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{35}FN_2O_2 + H)^+$): 403.

Example 4 (comparative)

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R,3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide and (2R)-N-[1-(4-methyl-3-pentenyl)-piperidin-4-yl]-2-[(1R,3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0092] Structural formulae



[0093] The title compounds were prepared using (2R)-2-[(1R)-3-fluorocyclopenlyl]-2-hydroxy-2-phenylacetic acid, in the same manner as described in step 3 in Example 1, and separated in the final step.

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R,3S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0094] ^{1}H-NMR ($CDCl_3$, δ ppm) : 1.60 (3H, s), 1.70 (3H, s) , 1.38-2.17 (14H, m) , 2.27-2.32 (2H, m) , 2.70-2.81 (2H, m), 3.19-3.32 (1H, m), 3.63-3.74 (1H, m), 3.93 (1H, brs), 5.00-5.21 (2H, m), 5.96-6.02 (1H, m), 7.26-7.38 (3H m), 7.55-7.58 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{35}FN_2O_2 + H)^+$): 403

(2R)-N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-[(1R,3R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetamide

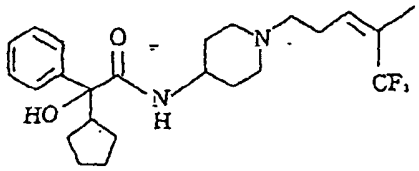
[0095] ^{1}H-NMR ($CDCl_3$, δ ppm) : 1.60 (3H, s), 1.68 (3H, s), 1.38 - 2.32 (6 H, m) , 2.74-2.88 (2H, m), 3.41-3.52 (1H, m), 3.63-3.74 (1H, m) , 5.02-5.21 (2H, m) , 6.90 (1H, d, J = 8.2Hz), 7.23-7.35 (3H, m), 7.66-7.69 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{35}FN_2O_2 + H)^+$): 403.

Example 5 (comparative)

N-[1-[(3Z)-4-trifluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

[0096] Structural formula



Step 1. Synthesis of N-(piperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide

[0097] To a solution of 3.51 g of 2-cyclopentyl-2-hydroxy-2-phenylacetic acid in 40 ml of N,N-dimethylformamide, 2.63 g of 1,1'-carbonyldiimidazole was added and stirred at room temperature for 2 hours. To the reaction mixture 3.96 g of 4-amino-1-(t-butoxycarbonyl)-piperidine monohydrochloride, 200 mg of 4-dimethylaminopyridine and 6.9 ml of diisopropylethylamine were added, followed by stirring overnight at room temperature. Saturated aqueous sodium bicarbonate solution was added to the reaction mixture followed by an extraction with diethyl ether. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Distilling the solvent off under reduced pressure, the resultant residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 3/1) to provide 2.84 g of a white solid. The solid was dissolved in 30 ml of 10% hydrochloric acid-methanol, and stirred overnight at room temperature. Distilling the methanol off under reduced pressure, the residue was diluted with water and washed with diethyl ether. The aqueous layer was made basic with sodium hydroxide and extracted with chloroform. The organic layer was washed with water and then with brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 2.15 g of the title compound was obtained as a white solid.

Step 2. Synthesis of (3Z)-4-trifluoromethyl-3-pentenylt-butyldiphenylsilyl ether

[0098] To a solution of 2.94 g of (3-t-butyldiphenylsilyl oxypropyl)triphenylphosphonium bromide in 40 ml of tetrahydrofuran, 2.5 ml of 1.7 M hexane solution of n-butyllithium was added dropwise at -78°C. The temperature was raised to -20°C. After stirring for an hour at said temperature, reaction mixture was cooled to -78°C into which 0.5 ml of

trifluoroacetone was added dropwise, followed by stirring overnight while raising the temperature to room temperature. The reaction liquid was diluted with hexane, washed with 10% hydrochloric acid, water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 9/1) to provide 1.44 g of the title compound.

Step 3. Synthesis of (3Z)-4-trifluoromethyl-3-pentenol

[0099] To a solution of 1.44 g of (3Z)-4-trifluoromethyl-3-pentenyl t-butyl-diphenylsilyl ether in 8 ml of tetrahydrofuran, 4.4 ml of 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran was added, followed by stirring for 2 hours at room temperature. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: ethyl acetate) to provide 414 mg of the title compound.

Step 4. Synthesis of (3Z)-4-trifluoromethyl-3-pentenyl p-toluenesulfonate

[0100] To a solution of 414 mg of (3Z)-4-trifluoromethyl-3-pentenol in 6 ml of pyridine, 565 mg of p-toluenesulfonyl chloride was added under cooling with ice, followed by stirring for 16 hours at room temperature. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 9/1) to provide 412 mg of the title compound.

Step 5. Synthesis of N-[1-[(3Z)-4-trifluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

[0101] To a solution of 77 mg of N-(piperidin-4-yl)-2-cyclopentyl-2-hydroxy-2-phenylacetamide in 3 ml of N,N-dimethylformamide, 74 mg of (3Z)-4-trifluoromethyl-3-pentenyl p-toluenesulfonate, 102 mg of potassium carbonate and 43 mg of potassium iodide were added by the order stated at room temperature, followed by 3 hours' heating under reflux. The reaction liquid was diluted with diethyl ether, washed with water and saturated saline solution by the order stated, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by preparative thin layer chromatography (Kieselgel™ 60F_{254}, Art 5744 (Merck) chloroform / methanol = 9/1) to provide 27 mg of the title compound as an oily substance.

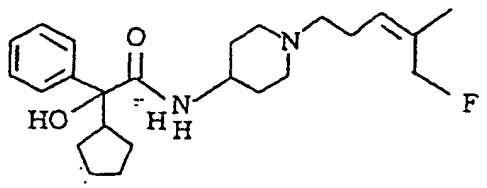
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.12-1.88 (1 6H, m) , 1.83 (3H, s) , 2.01 - 2.13 (2H, m) , 2.68-2.80 (2H, m) , 2.97-3.10 (1H, m) , 3.13 (1H, brs) , 3.62-3.76 (1H, m) , 5.65-5.72 (1H, m) , 6.32 (1H, d, J = 8. 5Hz) , 7.23-7.36 (3H, m) , 7.59 (2H, d, J=7.3Hz)

low resolution FAB-MS (m/e, ($C_{24}H_{33}F_3N_2O_2$ + H)$^+$): 439.

Example 6 (comparative)

N-[1-[(3Z)-4-fluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

[0102] Structural formula



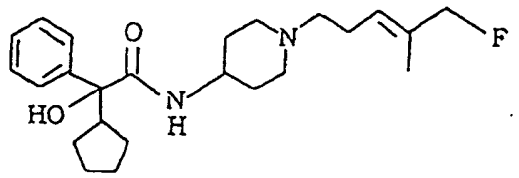
[0103] The title compound was prepared by the procedures similar to steps 2-5 of Example 5, using fluoroacetone.

^{1}H-NMR ($CDCl_3$, δ ppm): 1.04-2.16 (14H, m), 1.79 (3H, s), 2.16-2.28 (2H, m), 2.28-2.40 (2H, m), 2.66 - 2.86 (2H, m) , 2.94-3.24 (2H, m) , 3.62-3.78 (1H, m), 4.86 (2H, d, J=47.5Hz), 5.34-5.44 (1H, m) , 6.36 (1H, d, J=8. 3Hz), 7.22-7.40 (3H, m), 7.56-7.64 (2H, m)

Example 7 (comparative)

N-[1-[(3E)-4-fluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl]-2-hydroxy-2-phenylacetamide

[0104] Structural formula



Step 1. Synthesis of (2E) -5 -bromo -2-methyl-2 -pentenol

[0105] To a solution of 681 mg of selenium dioxide in 10 ml of dichloromethane, 2.5 ml of t-butyl peroxide was added at room temperature, stirred for 30 minutes at said temperature, and further 2.0 g of 5-bromo-2-methyl-2-pentene was added, followed by stirring for 2 hours. The reaction mixture was diluted with diethyl ether, washed with aqueous sodium thiosulfate solution, 10% aqueous potassium hydroxide solution, and then with brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 20/1 - 4/1) to provide 1.24 g of the title compound.

Step 2. Synthesis of (2E)-5-bromo-2-methyl-2-pentenylt-butyldimethylsilyl ether

[0106] To a solution of 300 mg of (2E)-5-bromo-2-methyl-2-pentenol in 10 ml of N,N-dimethylformamide, 302 mg of t-butyldimethylsilyl chloride and 137 mg of imidazole were added, followed by stirring for an hour at room temperature. The reaction liquid was diluted with diethyl ether, washed with water and then with brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 604 mg of the title compound was obtained.

Step 3. Synthesis of N-[1-[(3E)-4-t-butyldimethylsilyloxymethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

[0107] The title compound was prepared by the method similar to step 5 of Example 5, using (2E)-5-bromo-2-methyl-2-pentenyl t-butyldimethylsilyl ether.

Step 4. Synthesis of N-[1-[(3E)-4-fluoromethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide

[0108] To a solution of 59 mg of tetrabutylammonium fluoride trihydrate in 3 ml of tetrahydrofuran, 200 mg of molecular sieves 4A, 31 mg of N-[1-[(3E)-4-t-butyldimethylsilyloxymethyl-3-pentenyl]piperidin-4-yl]-2-cyclopentyl-2-hydroxy-2-phenylacetamide and 22 mg of p-toluenesulfonyl fluoride were added sequentially, followed by overnight heating under reflux at 80°C. After removal of the insoluble material by filtration, the solvent was distilled off under reduced pressure. The remaining residue was purified by preparative thin layer chromatography [Kieselgel™ $60F_{254}$, Art 5744 (Merck); chloroform / methanol = 20/1], to provide 11 mg of the title compound as an oily substance.

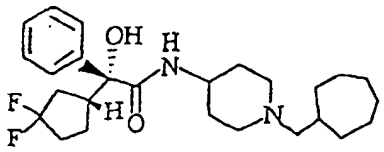
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.10-1.76 (10H, m) , 1.70 (3H, s) , 1.76 - 1.95 (2H, m) , 1.95-2.4 2 (6H, m) , 2.72 - 2.88 (2H, m) , 2.94-3.24 (2H m) , 3.62-3.78 (1H, m) , 4.69 (2H, d, J = 47.8Hz), 5.44-5.54 (1H, m) , 6.37 (1H, d, J = 8.0Hz), 7.22 -7.40 (3H, m) , 7.56-7.64 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{35}FN_2O_2 + H)^+$): 403

Example 8 (comparative)

(2R)-N-(1-cycloheptylmethylpiperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0109] Structural formula



[0110] The title compound was prepared by a method similar to the steps 1 and 5 of Example 5, using (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid and cycloheptylmethyl methanesulfonate.

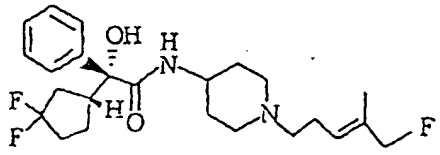
^{1}H-NMR ($CDCl_3$, δ ppm): 1.03 - 2.27 (27H, m) 2.63-2.71 (2H, m), 3.21-3.33 (1H, m), 3.49 (1H, brs), 3.61-3.72 (1H, m), 6.23 (1H, d, J=8.3Hz), 7.27-7.39 (3H, m), 7.53-7.57 (2H m)

low resolution FAB-MS (m/e, $(C_{26}H_{38}F_2N_2O_2 + H)^+$) : 449.

Example 9 (comparative)

(2R)-N-[1-[(3E)-4-fluoromethyl-3-pentenyl]-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0111] Structural formula



[0112] The title compound was prepared by a method similar to Example 7, using (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

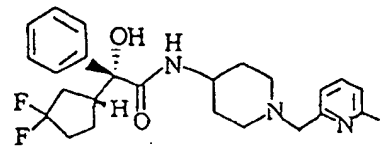
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.34-1.52 (2 H, m) , 1.69 (3 H, s) , 1.75-2.31 (12H, m) , 2.31-2.46 (2H, m), 2.72-2.86 (2H, m), 3.24 -3.38 (1H, m) , 3.43 (1H, brs), 3.62-3.78 (1H, m) , 4.69 (2H, d, J=47.8Hz), 5.42-5.52 (1H, m), 6.34 (1H, d, J=7.9Hz), 7.24-7.42 (3H, m), 7.52-7.60 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{33}F_3N_2O_2 + H)^+$) : 439.

Example 10

(2R)-N-[1-(6-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0113] Structural formula



Step 1. Synthesis of (2R)-N-(piperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0114] The title compound was prepared by a method similar to the step 1 of Example 5, using (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

Step 2. Synthesis of (2R)-N-[1-(6-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

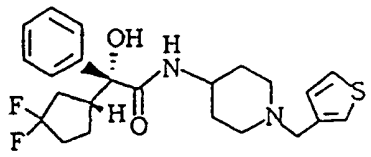
[0115] To a solution of 17 mg of (2R)-N-(piperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide in 2 ml of tetrahydrofuran, 3 μl of acetic acid, 12 mg of 6-methylpyridine-2-carbaldehyde and 21 mg of sodium triacetoxyborohydride were added sequentially at room temperature, and stirred overnight at the same temperature. The reaction mixture was diluted with ethyl acetate, washed with brine and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by preparative thin layer chromatography (Kiesel-gel™ $60F_{254}$, Art 5744 (Merck) chloroform / methanol = 10/1) to provide 9 mg of the title compound as a solid substance.

^{1}H-NMR ($CDCl_3$, δ ppm) : 1.35-1.50 (2H, m), 1.72-2.23 (10H, m), 2.53 (3H, s), 2.70-2.80 (2H, m), 3.21-3.35 (1H, m), 3.59 (2H, s), 3.60-3.78 (1H, m), 6.31 (1H, d, J = 8.5Hz), 7.02 (1H, t, J = 7.6Hz), 7.18 (1H, d, J=7.6Hz), 7.28-7.39 (3H, m), 7.50 (1H, d, J=7.6Hz), 7.53-7.59 (2H, m)

Example 11

(2R)-N-[1-(3-thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0116] Structural formula



[0117] The title compound was prepared by a method similar to the step 2 of Example 10 using thiophene-3-aldehyde.

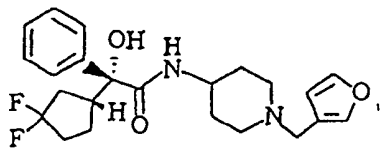
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.30-1.50 (2H, m) , 1.56-2.30 (10H, m) , 2.66-2.82 (2H, m) , 3.22-3.37 (1H, m) , 3.40 (1H, s) , 3.49 (2H, s) , 3.61-3.78 (1H, m) , 6.25 (1H, d, J = 8.2Hz) , 7.02 (1H, dd, J = 1.1Hz, 7.6Hz) , 7.06-7.12 (1H, m) , 7.22-7.42 (4H, m) , 7.50-7.60 (2H, m)

low resolution FAB-MS (m/e, $(C_{23}H_{28}F_2N_2O_2S + H)^+$) : 435.

Example 12

(2R)-N-[1-(3-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0118] Structural formula



[0119] The title compound was prepared by a method similar to the step 2 of Example 10, using furan-3-aldehyde.

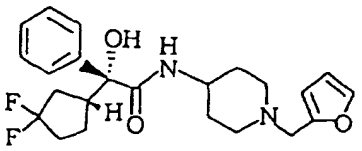
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.32-1.47 (2H, m) , 1.73-2.27 (10H, m) , 2.70-2.78 (2H, m), 3.24-3.35 (1H, m), 3.33 (2H, s), 3.42 (1H, s), 3.62-3.75 (1H, m), 6.26 (1H, d, J = 7.2Hz), 6.34 (1H, s) , 7.27-7.40 (5H, m), 7.52-7.57 (2H, m)

low resolution FAB-MS (m/e, $(C_{23}H_{28}F_2N_2O_3 + H)^+$): 419.

Example 13

(2R)-N-[1-(2-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0120] Structural formula

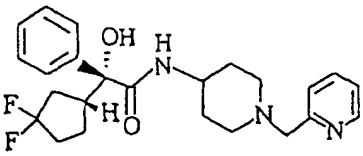


[0121] The title compound was prepared by a method similar to the step 2 of Example 10, using furan-2-aldehyde. ^{1}H-NMR ($CDCl_3$, δ ppm) : 1.35-1.49 (2H, m) , 1.73-2.25 (10H, m) , 2.70-2.80 (2H, m), 3.23-3.35 (1H, m), 3.48 (1H, s), 3.49 (2H, s), 3.61-3.73 (1H, m), 6.17 (1H, d, J =3.0Hz), 6.27-6.31 (2H, m) , 7.27-7.38 (4H, m), 7.52-7.56 (2H, m)
low resolution FAB-MS (m/e, $(C_{23}H_{28}F_2N_2O_3 + H)^+$): 419.

Example 14

(2R)-N-[1-(2-pyridylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0122] Structural formula

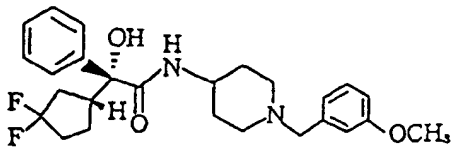


[0123] The title compound was prepared by a method similar to the step 2 of Example 10, using pyridine-2-aldehyde. ^{1}H-NMR ($CDCl_3$, δ ppm) : 1.39-1.52 (2H, m), 1.75-2.25 (10H, m), 2.70-2.80 (2H, m), 3.24-3.36 (1H, m), 3.58 (1H, s), 3.61 (2H, s), 3.67-3.77 (1H, m), 6.32 (1H, d, J =7.8Hz), 7.15 (1H, ddd, J=1.2Hz, 4.8Hz, 7.6Hz), 7.27-7.39 (4H, m), 7.53-7.57 (2H, m), 7.63 (1H, td, J=1. 8Hz, 7.6Hz), 8.52 (1H, ddd, J=1.2Hz, 1.8Hz, 3.0Hz)
low resolution FAB-MS (m/e, $(C_{24}H_{29}F_2N_3O_2 + H)^+$) : 430.

Example 15

(2R)-N-[1-(3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0124] Structural formula



[0125] To a solution of 71 mg of (2R)-N-(piperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide in 2 ml of N,N-dimethylformamide, 74 mg of 3-methoxybenzyl chloride and 80 mg of potassium carbonate were added at room temperature, followed by stirring for about 12 hours. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by preparative thin layer chromatography (Kieselgel™ 60F_{254}, Art 5744 (Merck)

chloroform / methanol = 9/1) to provide 75 mg of the title compound as a white solid.

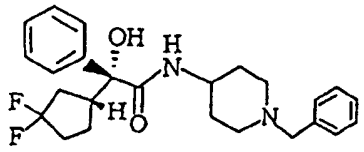
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.32-1.54 (2H, m) , 1.65-2.30 (10H, m) , 2.68-2.85 (2H, m) , 3.21-3.39 (1H, m) , 3.42 (1H, s) 3.45 (2H, s) , 3.62-3.78 (1H, m) , 3.80 (3H, s) , 6.27 (1H, d, J = 8.2Hz) , 6.76-6.83 (1H, m), 6.84-6. 90 (2H, m) , 7.21 (1H, t, J=8. 0Hz), 7.24-7.40 (3H, m) , 7.51-7.59 (2H, m)

low resolution FAB-MS (m/e, $(C_{26}H_{32}F_2N_2O_3 + H)^+$) : 459.

Example 16

(2R)-N-(1-benzylpiperidin-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0126] Structural formula



[0127] The title compound was prepared in the same manner as described in Example 15 using benzyl bromide.

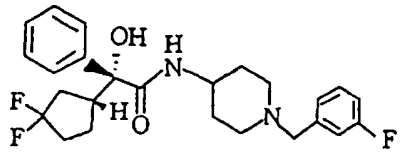
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.35-1.52 (2H, m), 1.70-2.23 (10H, m), 2.70-2.81 (2H, m), 3.32-3.34 (1H, m), 3.41 (1H, s) 3.48 (2H, s), 3.60-3.80 (1H, m), 6.27 (1H, d, J =8.0Hz), 7.24-7.39 (8H, m), 7.54-7.56 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{30}F_2N_2O_2 + H)^+$) : 429.

Example 17

(2R)-N-[1-(3-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0128] Structural formula



[0129] The title compound was prepared in the same manner as described in Example 15 using 3-fluorobenzyl chloride.

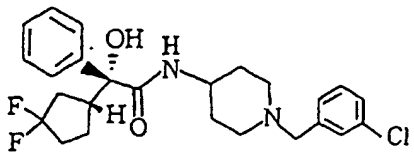
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.34-1.52 (2H, m) , 1.52-2.30 (10H, m) , 2.65-2.80 (2H, m), 3.22-3.38 (1H, m) , 3.40 (1H, s) 3.72 (2H, s) , 3.60-3. 80 (1H, m) , 6.28 (1H, d, J = 7.7Hz), 6.88-6.97 (1H, m) , 7.00-7.10 (2H, m), 7.20-7.42 (4H, m), 7.51-7.60 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{29}F_3N_2O_2 + H)^+$) : 447.

Example 18

(2R)-N-[1-(3-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0130] Structural formula



[0131] The title compound was prepared in the same manner as described in Example 15 using 3-chlorobenzyl chloride.

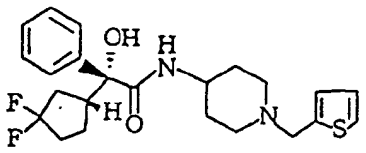
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.33-1.50 (2H, m), 1.60-2.25 (10H, m), 2.67-2.77 (2H, m), 3.24-3.38 (1H, m), 3.44 (2H, s) 3.63-3.76 (1H, m), 6.29 (1H, d, J=8. 0Hz), 7.13-7.40 (7H, m), 7.53-7.57 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{29}ClF_2N_2O_2 + H)^+$) : 463.

Example 19

(2R)-N-[1-(2-thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0132] Structural formula



[0133] The title compound was prepared in the same manner as described in Example 15 using 2-thienylmethyl chloride.

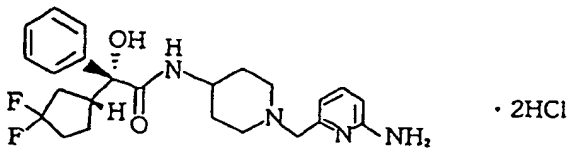
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.32-1.50 (2H, m) , 1.52-2.30 (10H, m) , 2.70-2.82 (2H, m) , 3.22-3.36 (1H, m) , 3.41 (1H, s) 3.62-3.76 (1H, m) , 3.68 (2H, s) , 6.26 (1H, d, J= 7.9Hz), 6.87 (1H, dd, J=3.2Hz, 4.8Hz), 6.92 (1H, dd, J = 3.2Hz, 4.8Hz) 7.21 (1H, dd, J=1.5Hz, 4.8Hz), 7.24-7.40 (3H, m), 7.50-7.58 (2H, m)

low resolution FAB-MS (m/e, $(C_{23}H_{28}F_2N_2O_2S + H)^+$) : 435.

Example 20

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0134] Structural formula



· 2HCl

[0135] The compound of Example 20 was prepared by the following methods 1, 2 and 3.

Method 1:

Step 1. Synthesis of 6 -tert-butyldiphenylsilyloxymethylpyridine-2-carboxylic acid

[0136] To a solution of 1.8 g of ethyl 6-hydroxymethylpyridine-2-carboxylate in 55 ml of N,N-dimethylformamide, 1.4 g of imidazole and 3. 9 g of tert-butyldiphenylsilane chloride were added under cooling with ice, sequentially, followed

by stirring for 12 hours at room temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution, water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was dissolved in 60 ml of methanol. To the solution 7.5 ml of 4N aqueous sodium hydroxide solution was added, stirred for 20 hours at room temperature and for further 2 hours at 60°C. Distilling the methanol off under reduced pressure, the residue was made acidic with 1N hydrochloric acid. The system was extracted with chloroform, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 4/1) to provide 895 mg of the title compound as a white solid.

Step 2. Synthesis of 6-tert-butyloxycarbonylaminopyridin-2-ylmethyl tert-butyldiphenylsilyl ether

[0137] To a solution of 890 mg of the 6-tert-butyldiphenylsilyloxymethylpyridine-2-carboxylic acid as obtained in above step 1 in 30 ml of toluene, 0.63 ml of triethylamine, 3.2 ml of tert-butanol and 887 mg of diphenylphosphorylazide were added sequentially at room temperature, followed by heating for 16 hours at 100°C under stirring. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, 10% aqueous citric acid solution, water and then brine, and dried over anhydrous magnesium sulfate. After the solvent was distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 4/1) to provide 863 mg of the title compound as an oily substance.

Step 3. Synthesis of 6 -tert-butyloxycarbonylaminopyridine-2-methanol

[0138] The title compound was prepared in the same manner as described in the step 3 of Example 5 using the 6-tert-butyloxycarbonylaminopyridin-2-ylmethyl tert-butyldiphenylsilyl ether as obtained in above step 2.

Step 4. Synthesis of 6-tert-butyloxycarbonylaminopyridin-2-ylmethyl methanesulfonate

[0139] To a solution of 61 mg of the 6-tert-butyloxycarbonylaminopyridine-2-methanol as obtained in above step 3 in 2 ml of chloroform, 0.19 ml of triethylamine and 0.032 ml of methanesulfonyl chloride were added under cooling with ice, followed by stirring for an hour at the same temperature. The reaction liquid was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution, water and brine by the order stated and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 124 mg of the title compound as an oil.

Step 5. Synthesis of (2R)-N-[1-(6-tert-butyloxycarbonylaminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0140] The title compound was prepared in the same manner as described in Example 15 using the 6-tert-butyloxycarbonylaminopyridin-2-ylmethyl methanesulfonate as obtained in the step 4 above.

Step 6. Synthesis of (2R)-N-[1-(6-aminopyridin-2-yl-methyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0141] The title compound was obtained as a white solid, upon treating the (2R)-N-[1-(6-tert-butyloxycarbonylaminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in above step 5 with hydrochloric acid according to usual manner.

^{1}H-NMR (CD_3OD, δ ppm) : 1.76-2.14 (10H, m) , 3.20-3.63 (5H, m) , 3.85-4.00 (1H, m), 4.44 (2H, s), 7.07-7.34 (2H, m), 7.25-7.34 (3H, m), 7.58-7.60 (2H, m), 7.89-7.94 (1H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{30}F_2N_4O_2 + H)^+$) : 445.

Method 2:

Step 1. Synthesis of ethyl 6-tert-butyloxycarbonylaminopyridine-2 -carboxylate

[0142] The title compound was prepared in the same manner described in the step 2 of above method 1, using 6-ethoxycarbonylpyridine-2-carboxylic acid.

Step 2. Synthesis of 6 -tert-butyloxycarbonylaminopyridine-2-methanol

[0143] To a solution of 500 mg of calcium chloride in 10 ml of ethanol, 150 mg of sodium borohydride was added

under cooling with ice, followed by stirring for 15 minutes at the same temperature. To the reaction mixture 1.1 g of the ethyl 6-tert-butyloxycarbonylaminopyridine-2-carboxylate as obtained in above step 1 was added and stirred for 13 hours at room temperature. The ethanol was distilled off under reduced pressure, and the residue was suspended in chloroform-water mixture to be removed of insoluble material. The organic layer was washed with water and then brine and dried over anhydrous magnesium sulfate. Thus 996 mg of the title compound was obtained as a light yellow oil.

Step 3. Synthesis of 4-tert-butyloxycarbonylamino-1-(6-tert-butyloxycarbonylaminopyridin-2-ylmethyl)piperidine

[0144] The title compound was prepared by a method similar to the steps 4 to 5 of above production method 1 using the 6-tert-butyloxycarbonylaminopyridine-2-methanol as obtained in the above step 2 and 4-tert-butyloxycarbonylaminopiperidine.

Step 4. Synthesis of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0145] 163 mg of the 4-tert-butyloxycarbonyl-amino-1-(6-tert-butyloxycarbonylaminopyridin-2-ylmethyl)piperidine as obtained in above step 3 was dissolved in 5 ml of 10% HCl-methanol solution, followed by stirring for 13 hours at 40°C. Distilling the methanol off under reduced pressure, the remaining residue was suspended in 15 ml of chloroform, to which 0.16 ml of triethylamine, 86 mg of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, 114 mg of hydroxybenzotriazole and 75 mg of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide were added under cooling with ice sequentially, followed by stirring for 1.5 hours at room temperature. The reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate solution and then brine, and dried over anhydrous magnesium sulfate. After the solvent was distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: chloroform / methanol = 50/1 to 20/1) to obtain 101 mg of the title compound as a white solid.

^{1}H-NMR (CDC l_3, δ ppm) : 1.35-1.51 (2H, m), 1.70-2.25 (10H, m), 2.68-2.80 (2H, m), 3.21-3.35 (1H, m), 3.41 (2H, s), 3.52 (1H, brs) , 3.62-3.77 (1H, m) , 4.40 (2H, brs), 6.28 (1H, d, J=8.2Hz) , 6.36 (1H, d, J=8.2Hz), 6.67 (1H, d, J=7.3Hz), 7. 27-7.40 (4H, m) , 7.53-7.57 (2H, m)

Step 5. Synthesis of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0146] The title compound was prepared by treating the (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in the above step 4 with hydrochloric acid according to the accepted practice.

Method 3:

Step 1. Synthesis of 2-tert-butyloxycarbonylamino-6-methylpyridine

[0147] To a solution of 2 g of 6-methyl-2-aminopyridine in 30 ml of chloroform, 5 g of di-tert-butyloxydicarbonate was added at room temperature. Then the mixture was heated to 70°C, to which 2.5 g of 4-dimethylaminopyridine was added, followed by stirring for 2 hours at the same temperature. After the solvent was distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 20/1) to provide 4.1 g of the title compound as a white solid.

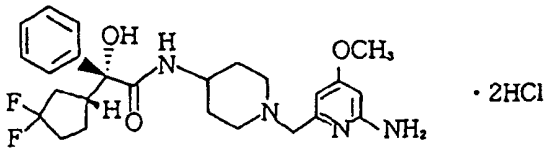
Step 2. Synthesis of (2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0148] To a solution of 100 mg of the 2-tert-butyloxycarbonylamino-6-methylpyridine as obtained in above step 1 in 3 ml of carbon tetrachloride, 90 mg of N-bromosuccinimide and 10 mg of benzoyl peroxide were added sequentially at room temperature, followed by heating for 6 hours under reflux with stirring. Filtering the insoluble materials off, the solvent was distilled off under reduced pressure. The title compound was prepared by a method similar to the step 5 of method 1 and the steps 4-5 of the method 2, using the resulting residue and 4-tert-butyloxycarbonylaminopiperidine.

Example 21

(2R)-N-[1-(6-amino-4-methoxypyridin-2-ylmethyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0149] Structural formula



[0150] The title compound was prepared by a method similar to Example 20, using ethyl 6-hydroxymethyl-4-methoxypyridine-2-carboxylate.

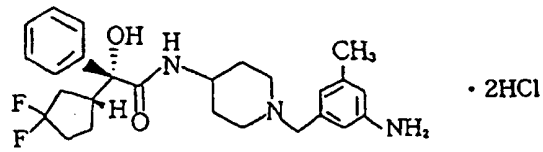
^{1}H-NMR (CD_3OD, δ ppm) : 1.69-2.21 (10H, m) , 3.10-3.70 (5H, m), 3.83 - 3.97 (1H, m) , 3.98 (3H, s) , 4.30-4.46 (2H, m) , 6.39-6.47 (1H, m) , 6.74-6.89 (1H, m) , 7.20-7.38 (3H, m) , 7.58 (2H, d, J=6.9Hz)

low resolution FAB-MS (m/e, $(C_{25}H_{32}F_2N_4O_3 + H)^+$) : 475.

Example 22

(2R)-N-[1-(3-amino-5-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0151] Structural formula



Step 1. Synthesis of N-(tert-butyloxycarbonyl)-3,5-dimethylaniline

[0152] To a solution of 1.2 g of 3,5-dimethylaniline in a liquid mixture of 20 ml of dioxane and 10 ml of 10% aqueous sodium hydroxide solution, 2.7 g of di-tert-butyl-dicarbonate were added, followed by heating for 1.5 hours at 100°C with stirring. The reaction mixture as diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. After the solvent was distilled off under reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 9/1) to provide 1.8 g of the title compound as an oil.

Step 2. Synthesis of 3-(tert-butyloxycarbonylamino)-5-methylbenzyl bromide

[0153] To a solution of 1.8 g of the N-(tert-butyloxycarbonyl)-3,5-dimethylaniline as obtained in above step 1 in 20 ml of carbon tetrachloride, 1.5 g of N-bromosuccinimide and 53 mg of 2,2'-azobis(isobutyronitrile) were added, followed by heating for 3 hours at 100°C under stirring. The reaction mixture was diluted with hexane, filtered and the solvent was distilled off under reduced pressure to provide 2.8 g of the title compound as an oil.

Step 3. Synthesis of (2R)-N-[1-(3-amino-5-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0154] The title compound was prepared by a method similar to the steps 5-6 of the production method 1 of Example 20, using the 3-(tert-butyloxycarbonylamino)-5-methylbenzyl bromide as obtained in above step 2.

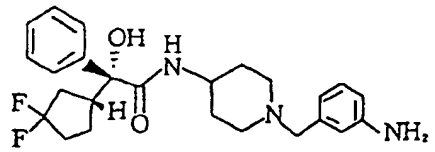
^{1}H-NMR (CD_3OD, δ ppm) : 1.66-2.11 (12H, m), 2.99-3.48 (3H, m) , 3.26 (3H, s) , 3.78-3.98 (1H, m), 4.28 (2H, s), 7.18-7.60 (8H, m)

low resolution FAB-MS (m/e, $(C_{26}H_{33}F_2N_3O_2 + H)^+$) : 458.

Example 23

(2R)-N-[1-(3-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0155] Structural formula



Step 1. Synthesis of (2R)-N-[1-(3-nitrobenzyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0156] The title compound was prepared by a method similar to Example 15, using 3-nitrobenzyl chloride.

Step 2. Synthesis of (2R)-N-[1-(3-aminobenzyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0157] 6.5 mg of the (2R)-N-[1-(3-nitrobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in above step 1 was heated to 60°C together with 2 mg of iron powder in aqueous ethanol. After adding thereto 1 drop of conc. hydrochloric acid, the heating was continued at 100°C for about 1 hour under stirring. The reaction mixture was made basic with 4N aqueous sodium hydroxide solution and extracted with chloroform. The organic layer was dried over anhydrous sodium sulfate, and the solvent was distilled off under reduced pressure to provide 4.8 mg of the title compound as a white solid.

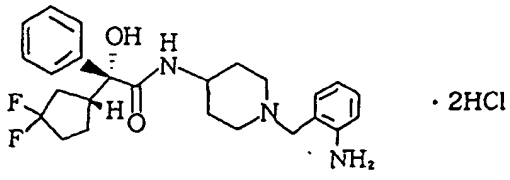
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.30-1.48 (2H, m), 1.50-2.25 (10H, m), 2.68-2.78 (2H, m), 3.24-3.40 (1H, m), 3.38 (2H, s), 3.43 (1H, s) , 3.52-3.80 (1H, m) , 6.26 (1H, d, J =7. 9Hz), 6.57 (1H, dd, J = 1.5Hz, 7.8Hz), 6.65 (1H, d, J = 1.5Hz), 6.66 (1H, d, J=7.8Hz), 7.08 (1H, t, J = 7.8Hz) , 7.28-7.39 (3H, m), 7.53-7.57 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{31}F_2N_3O_2 + H)^+$) : 444.

Example 24

(2R)-N-[1-(2-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0158] Structural formula



[0159] The title compound (free base) was obtained by a method similar to Example 23, using 2-nitrobenzyl chloride, which was treated with hydrochloric acid and to provide the title compound.

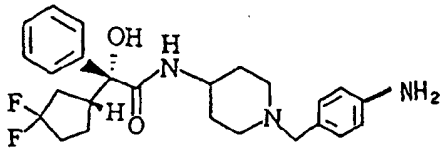
^{1}H-NMR (CD_3OD, δ ppm) : 1.50-1.95 (10H, m) , 2.92-3.07 (2H, m) , 3.07-3.20 (1 H, m) , 3.24-3.38 (2H, m) , 3.67-3.80 (1H, m) , 4.15-4.27 (2H, m) , 7.05-7.45 (9H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{31}F_2N_3O_2 + H)^+$): 444.

Example 25

(2R)-N-[1-(4-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0160] Structural formula

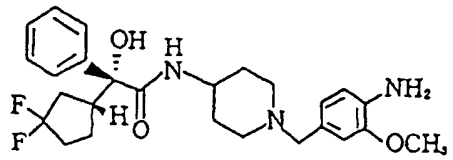


[0161] The title compound was prepared by a method similar to Example 23, using 4-nitrobenzyl chloride.
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.35-1.52 (2H, m), 1.70-2.23 (10H, m), 2.70-2.82 (2H, m), 3.23-3.35 (1H, m) , 3.41 (2 H, s), 3.30-3.70 (3H, m), 3.65-3.75 (1H, m), 6.29 (1H, d, J=7.4Hz), 6.63 (2H, d, J=8.5Hz), 7.06 (2H, d, J=8.5Hz), 7.28-7.39 (3H, m), 7.52-7.56 (2H, m)
low resolution FAB-MS (m/e, $(C_{25}H_{31}F_2N_3O_2 + H)^+$) : 444.

Example 26

(2R)-N-[1-(4-amino-3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0162] Structural formula

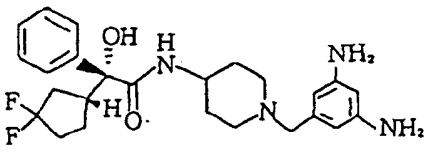


[0163] The title compound was prepared by a method similar to Example 23, using 3-methoxy-4-nitrobenzyl chloride.
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.35-1.60 (2H, m) , 1.70-2.30 (10H, m) , 2.70-2.90 (2H, m) , 3.22-3.38 (1H, m) , 3.44 (2H, s) , 3.40-3.60 (1H, m), 3.62-3.85 (3H, m) , 3.85 (3H, s) , 6.36 (1H, d, J=7. 9Hz) , 6.60-6.70 (2H, m) , 6.81 (1 H, s) , 7.24-7.40 (3H, m) , 7.51-7.58 (2H, m)
low resolution FAB-MS (m/e, $(C_{26}H_{33}F_2N_3O_3 + H)^+$) : 474.

Example 27

(2R)-N-[1-(3,5-diaminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0164] Structural formula



[0165] The title compound was prepared by a method similar to Example 23, using 3,5-dinitrobenzyl chloride.
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.30-2.20 (1 2H, m) , 2.70-2.80 (2H, m) , 3.23-3.36 (1H, m) , 3.28 (2H, s) , 3.44 (1H, s) , 3.60-3.73 (1H, m) , 5.93 (1H, t, J=2.0Hz), 6.07 (2H, d, J=2.0Hz), 6.23 (1 H, d, J=7.5Hz), 7.29-7.40 (3H, m) , 7.53-7.57

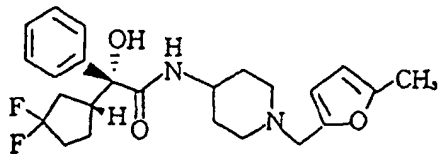
(2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{32}F_2N_4O_2 + H)^+$): 459.

Example 28

(2R)-N-[1-(5-methylfuran-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0166] Structural formula



Step 1. Synthesis of 4-(tert-butyloxycarbonylamino)-1-(5-methyl-2-furylmethyl)piperidine

[0167] To a solution of 200 mg of 4-(tert-butyloxycarbonylamino)piperidine in 5 ml of tetrahydrofuran, 0.1 ml of 5-methylfuran-3-aldehyde, 0.06 ml of acetic acid and 318 mg of sodium triacetoxyborohydride were added at room temperature, followed by stirring for 12 hours. To the reaction mixture, saturated aqueous sodium bicarbonate solution was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After distilling the solvent off under reduced pressure, the residue was recrystallized from ethyl acetate / n-hexane to provide 198 mg of the title compound.

Step 2. Synthesis of (2R)-N-[1-(5-methyl-2-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0168] To 88 mg of the 4-(tert-butyloxycarbonylamino)-1-(5-methyl-2-furylmethyl)piperidine as obtained in above step 1, 2 ml of 10% hydrogenchloride solution in methanol was added at room temperature, followed by stirring for about 12 hours. The solvent was distilled off under reduced pressure, and to a solution of the resultant residue in 4 ml of chloroform, 59 mg of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid, 93 mg of hydroxybenzotriazole, 0.2 ml of triethylamine and 66 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodimide were added sequentially at room temperature, followed by stirring for 2 hours. After addition of water, the reaction mixture was extracted with chloroform. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: chloroform / methanol = 50/1) to provide 63 mg of the title compound as a white solid.

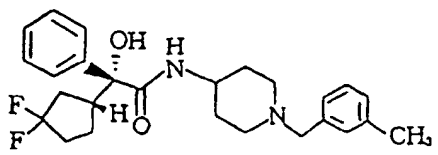
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.35-1.54 (2H, m), 1.60-2.25 (10H, m), 2.27 (3H, s), 2.71-2.86 (2H, m), 3.22-3.36 (1H, m), 3.40 (1H, s) , 3.45 (2H, s) , 3.60-3.76 (1H, m) , 5.85-5.90 (1H, m), 6.05 (1H, d, J=3.0Hz), 6.25 (1H, d, J=7.9Hz), 7.26-7.40 (3H, m), 7.50-7.56 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{30}F_2N_2O_3 + H)^+$) : 433.

Example 29

(2R)-N-[1-(3-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0169] Structural formula



Step 1. Synthesis of 4-(tert-butyloxycarbonylamino)-1-(3-methylbenzyl)piperidine

[0170] The title compound was prepared by a method similar to Example 15, using 4-(tert-butyloxycarbonylamino) piperidine and 3-methylbenzyl bromide.

Step 2. Synthesis of (2R)-N-[1-(3-methylbenzyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0171] The title compound was prepared by a method similar to Example 28, using the 4-(tert-butyloxycarbonylamino)-1-(3-methylbenzyl)piperidine as obtained in above step 1.

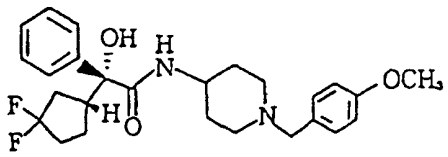
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.24-1.50 (2H, m), 1.50-2.25 (10H, m), 2.33 (3H, s), 2.60-2.82 (2H, m), 3.20-3.55 (3H, m), 3.42 (2H, s) , 6.25 (1H, d, J=8.1Hz), 7.00-7.14 (3H, m), 7.19 (1H, t, J = 7.6Hz), 7.23-7.42 (3H, m), 7.50-7.60 (2H, m)

low resolution FAB-MS (m/e, $(C_{26}H_{32}F_2N_2O_2 + H)^+$) : 443.

Example 30

(2R)-N-[1-(4-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0172] Structural formula



[0173] The title compound was prepared by a method similar to the step 2 of Example 10, using p-anisaldehyde.

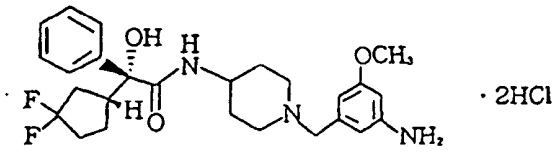
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.32-1.47 (2H, m) , 1.75-2.23 (10H, m), 2.65-2.76 (2H, m) , 3.22-3.36 (1H, m) , 3.42 (2H, s), 3.46 (1H, s), 3.63-3.76 (1H, m), 3.79 (3H, s), 6.27 (1H, d, J = 8.2Hz), 6.84 (2H, d, J = 8.6Hz), 7.19 (2H, d, J=8.6Hz) , 7.28-7.39 (3H, m) , 7.52-7.56 (2H, m)

low resolution FAB-MS (m/e, $(C_{26}H_{32}F_2N_2O_3 + H)^+$): 459.

Example 31

(2R)-N-[1-(3-amino-5-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0174] Structural formula



Step 1. Synthesis of methyl 3-tert-butoxycarbonylamino-5-methoxybenzoate

[0175] To a solution of 864 mg of methyl 3-methoxy-5-nitrobenzoate in 15 ml of methanol, 1.0 g of di-tert-butyldicarbonate and 912 mg of 10% palladium-on-carbon were added, followed by stirring for 7 hours at room temperature in a hydrogen atmosphere. The reaction liquid was filtered through Celite. Distilling the solvent off under reduced pressure, 1.28 g of the title compound was obtained as a white solid.

Step 2. Synthesis of 3 -tert-butoxycarbonylamino-5-methoxybenzyl alcohol

[0176] To a solution of 1.28 g of the methyl 3-tert-butoxycarbonylamino-5-methoxybenzoate as obtained in above step 1 in 8 ml of toluene, 12.1 ml of 1.0 M solution of diisobutylaluminum hydride in tetrahydrofuran was added at -78°C, followed by stirring for an hour at the same temperature. The reaction mixture was diluted with ethyl acetate, washed with water and then brine and dried over anhydrous magnesium sulfate. After distilling the solvent off under reduced pressure, the resulting residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 7/3) to provide 262 mg of the title compound as an oil.

Step 3. Synthesis of 3-tert-butoxycarbonylamino-5-methoxybenzaldehyde

[0177] To a solution of 194 mg of the 3-tert-butoxycarbonylamino-5-methoxybenzyl alcohol as obtained in above step 2 in 10 ml of chloroform, 1.89 g of manganese dioxide was added at room temperature, followed by stirring for 2 hours. The reaction mixture was filtered through Celite. Distilling the solvent off under reduced pressure, 132 mg of the title compound was obtained as an oily substance.

Step 4. Synthesis of (2R)-N-[1-(3-amino-5-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0178] The title compound was prepared by a method similar to the step 2 of Example 10 and the step 6 of method 1 of Example 20, using the 3-tert-butoxycarbonylamino-5-methoxybenzaldehyde as obtained in above step 3.

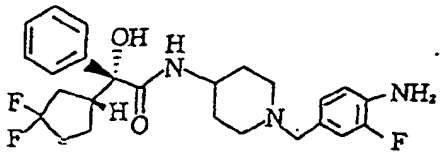
^{1}H-NMR (CD_3OD, δ ppm) : 1.74-2.14 (10H, m), 3.00-3.15 (2H, m), 3.27-3.52 (3H, m) , 3.82-3.92 (1H, m), 3.89 (3H, s) 4.32 (2H, s) , 7.01 (1H, s) , 7.18-7.35 (5H, m) , 7.56-7.60 (2H, m)

low resolution FAB-MS (m/e, $(C_{26}H_{33}F_2N_3O_3 + H)^+$) : 474.

Example 32

(2R)-N-[1-(4-amino-3-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0179] Structural formula



[0180] The title compound was prepared by a method similar to Example 22, using 3-fluoro-4-aminotoluene.

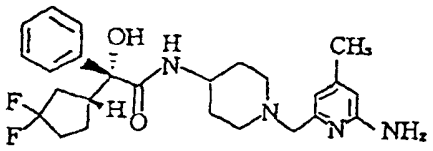
^{1}H-NMR ($CDCl_3$, δ ppm): 1.28-1.50 (2H, m), 1.50-2.32 (10H, m), 2.60-2.80 (2H, m), 3.20-3.38 (1H, m), 3.33 (2H, s), 3.45 (1H, s), 3.55-376 (3H, m), 6.25 (1H, d, J = 8.2Hz), 6.69 (1H, dd, J=8. 1,8. 9Hz), 6.82 (1H, dd, J=1. 6,8. 1Hz), 6.93 (1H, dd, J =1.6, 12.0Hz), 7.24-7.40 (3H, m), 7.50-7.58 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{30}F_3N_3O_2 + H)^+$) : 462.

Example 33

(2R)-N-[1-(6-amino-4-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0181] Structural formula



Step 1. Synthesis of 6-chloromethyl-4-methyl-2-acetylaminopyridine

[0182] To a solution of 23 mg of 6-acetylamino-4-methylpyridine-2-methanol in 2 ml of chloroform, 0.05 ml of thionyl chloride was added at room temperature, followed by heating for 15 minutes with stirring under reflux. Distilling the solvent off under reduced pressure, the title compound was obtained.

Step 2. Synthesis of (2R)-N-[1-(6-acetylamino-4-methylpyridin-2-yl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0183] The title compound was prepared by a method similar to Example 15, using the 6-chloromethyl-4-methyl-2-acetylaminopyridine as obtained in above step 1.

Step 3. Synthesis of (2R)-N-[1-(6-amino-4-methylpyridin-2-yl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0184] To a solution of 16.5 mg of the (2R)-N-[1-(6-acetylamino-4-methylpyridin-2-yl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide as obtained in above step 2 in 1 ml of methanol, 0.5 ml of 3M aqueous sodium hydroxide solution was added, and stirred for 1.5 hours at 60°C. The reaction liquid was diluted with diethyl ether, washed with water and brine by the order stated and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the resulting residue was purified by preparative thin-layer chromatography [Kieselgel™ $60F_{254}$, Art 5744 (Merck); chloroform / methanol = 10/1) to provide 14 mg of the title compound as an oily substance.

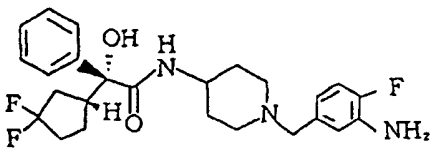
^{1}H-NMR ($CDCl_3$, δ ppm): 1.30-1.50 (2H, m), 1.71-2.30 (10H, m) , 2.33 (3H, s), 2.62-2.76 (2H, m), 3.21-3.38 (1H, m) , 3.29 (2H, s) , 3.60-3.78 (1H, m), 4.35-4.51 (2H, m) , 6.26 (1H, s), 6.35 (1H, d, J = 8.1Hz), 6.45 (1H, s), 7.25-7.40 (3H, m), 7.52-7.60 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{32}F_2N_4O_2 + H)^+$) : 459.

Example 34

(2R)-N-[1-(3-amino-4-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide dihydrochloride

[0185] Structural formula



[0186] The title compound was prepared by a method similar to Example 22, using 2-fluoro-5-methylaniline.

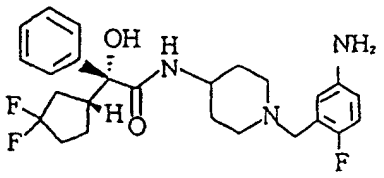
^{1}H-NMR (CD_3OD, δ ppm) : 1.68-2.11 (10H, m) , 3.00-3.50 (5H, m) , 3.79-3.90 (1H, m), 4.32 (2H, s), 7.1 8-7.30 (3H, m), 7.43 (1H, d, J=8. 4Hz) , 7.52-7.56 (2H, m) , 7.57-7.65 (1H, m) , 7.73-7.78 (1H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{30}F_3N_3O_2 + H)^+$) : 462.

Example 35

(2R)-N-[1-(5 -amino-2-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0187] Structural formula



[0188] The title compound was prepared by a method similar to the step 2 of Example 22 and Example 23, using 2-fluoro-5-nitrotoluene.

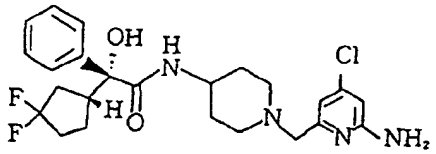
^{1}N-NMR ($CDCl_3$, δ ppm) : 1.36-1.49 (2H, m) , 1.57-2.26 (10H, m) , 2.71-2.78 (2H, m) , 3.24-3.36 (1H, m) , 3.42-3.57 (5H, m) , 3.66-3.75 (1H, m) , 6.24 (1H, d, J=8.1Hz), 6.51-6.56 (1H, m) , 6.65-6.68 (1H, m) , 6.82 (1H, t, J = 9.0Hz) , 7.29-7.40 (3H, m) , 7.53-7.57 (2H, m)

low resolution FAB-MS (m/e, ($C_{25}H_{30}F_3N_3O_2$ + H)$^+$) : 462.

Example 36

(2R)-N-[1-(2-amino-4-chloropyridin-6-ylmethyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0189] Structural formula



[0190] The title compound was prepared by a method similar to method 2 of Example 20, using methyl 4-chloro-6-hydroxymethylpyridine-2-carboxylate.

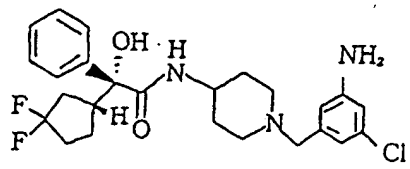
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.42-1.54 (2H, m) , 1.78-2.26 (10H, m), 2.76-2.79 (2H, m) , 3.28-3.38 (1H, m) , 3.42-3.47 (3H, m) , 3.67-3.75 (1H, m) , 4.53-4.56 (2H, m), 6.36 (1H, d, J=7. 2Hz), 6.38 (1H, d, J= 1.6Hz), 6.72 (1H, d, J=1.6Hz), 7. 25-7.39 (3H, m), 7.53-7.57 (2H, m)

low resolution FAB-MS (m/e, ($C_{24}H_{29}ClF_2N_4O_2$ + H)$^+$) : 479.

Example 37

(2R)-N-[1-(3-amino-5-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0191] Structural formula



Step 1. Synthesis of 3-chloro-5-nitrobenzyl methanesulfonate

[0192] To a solution of 92 mg of 3-chloro-5-nitrobenzyl alcohol in 3 ml of chloroform, 0.3 ml of triethylamine and 0.1 ml of methanesulfonyl chloride were added at room temperature, followed by stirring for 40 minutes, addition of saturated aqueous sodium bicarbonate solution and further stirring for 30 minutes. The reaction mixture was diluted with diethyl ether, washed with saturated aqueous sodium bicarbonate solution and then brine and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 119 mg of the title compound was obtained as an oil.

Step 2. Synthesis of (2R)-N-[1-(3-amino-5-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0193] The title compound was obtained by a method similar to Example 23, using the 3-chloro-5-nitrobenzyl methanesulfonate as obtained in above step 1.

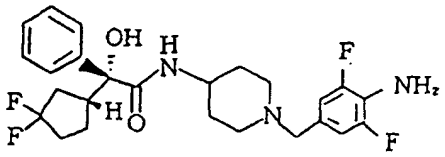
^{1}H-NMR ($CDCl_3$, δ ppm): 1.30-1.44 (2H, m) , 1.73-2.22 (10H, m) , 2.68-2.73 (2H, m) , 3.24-3.36 (1H, m) , 3.32 (2H, s) , 3.44 (1H, brs), 3.61-3.77 (3H, m) , 6.28 (1H, d, J=8.4Hz), 6.49 (1H, d, J=1.9Hz), 6.55 (1H, dd, J = 1.7, 1.9Hz), 6.66 (1H, d, J =1.7Hz), 7.29-7.39 (3H, m), 7.53-7.56 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{30}ClF_2N_3O_2 + H)^+$) : 459. 9.

Example 38

(2R)-N-[1-(4-amino-3,5-difluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0194] Structural formula



[0195] The title compound was prepared by a method similar to the step 2 of Example 10, using 4-amino-3,5-difluorobenzaldehyde.

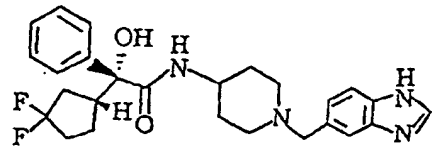
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.24-2.22 (12H, m), 2.66-2.72 (2H, m), 3.27-3.41 (4H, m), 3.66-3.71 (3H, m) , 6.28 (1H, d, J=7.8Hz), 6.77 (2H, d, J=8.3Hz), 7.28-7.39 (3H, m), 7.54-7.56 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{29}F_4N_3O_2 + H)^+$) : 480.

Example 39 (comparative)

(2R)-N-[1-(benzimidazol-5-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide

[0196] Structural formula



[0197] The title compound was prepared by a method similar to the step 2 of Example 10, using benzimidazole-5-carbaldehyde.

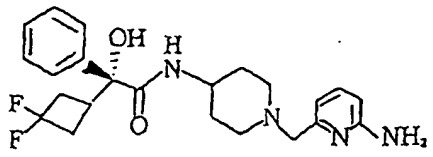
^{1}H-NMR (CD_3OD, δ ppm) : 1.45-2.25 (10H, m), 2.25-2.48 (2H, m) , 2.90-3.10 (2H, m), 3.20-3.42 (1H, m) , 3.56-3.75 (1 H, m), 3.82 (2H, s), 7.18-7.40 (4H, m), 7.51-7.75 (4H, m), 8.17 (1H, s)

low resolution FAB-MS (m/e, $(C_{26}H_{30}F_2N_4O_2 + H)^+$): 469.

Example 40 (comparative)

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-(3,3-difluorocyclobutyl)-2-hydroxy-2-phenylacetamide

[0198] Structural formula



[0199] The title compound was prepared by a method similar to the step 4 of method 2 of Example 20, using (2R)-2-(3,3-difluorocyclobutyl)-2-hydroxyphenylacetic acid and 4-amino-1-(6-aminopyridin-2-ylmethyl)piperidine trihydrochloride.

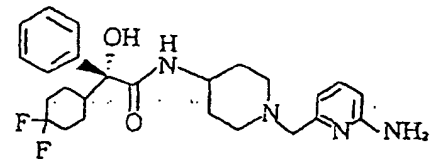
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.20-1.52 (2H, m) , 1.60-1.86 (2H, m) , 2.08-2.22 (2H, m) , 2.40-2.82 (6H, m) , 3.07-3.21 (1H, m) , 3.41 (2H, s), 3.60-3.80 (1H, m), 3.84 (1H, brs), 4.40 (2H, brs), 6.01 (1H, d, J = 8.1Hz), 6.36 (1H, d, J = 8.2Hz), 6.66 (1H, d, J = 8.2Hz), 7.28-7.42 (4H, m) , 7.43-7.50 (2H, m)

low resolution FAB-MS (m/e, $(C_{23}H_{28}F_2N_4O_2 + H)^+$): 431.

Example 41 (comparative)

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-(4,4-difluorocyclohexyl)-2-hydroxy-2-phenylacetamide

[0200] Structural formula



[0201] The title compound was prepared by a method similar to the step 4 of method 2 of Example 20, using (2R)-2-(4,4-difluorocyclohexyl)-2-hydroxyphenylacetic acid and 4-amino-1-(6-aminopyridin-2-ylmethyl)piperidine trihydrochloride.

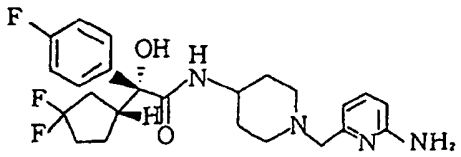
^{1}H-NMR ($CDCl_3$, δ ppm) : 1.20-1.97 (10H, m), 1.97-2.22 (4H, m), 2.44-2.68 (1H, m) , 2.70-2.92 (3H, m), 3.42 (2H, s), 3.62-3.80 (1H, m), 4.42 (2H, brs), 6.36 (1H, d, J=8.2Hz), 6.62 (1H, d, J=7.9Hz), 6.67 (1H, d, J=8.2Hz), 7.24-7.42 (4H, m), 7.55-7.62 (2H, m)

low resolution FAB-MS (m/e, $(C_{25}H_{32}F_2N_4O_2 + H)^+$) : 459.

Example 42

(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-(3,3-difluorocyclopentyl)-2-(4-fluorophenyl)-2-hydroxyacetamide

[0202] Structural formula



[0203] The title compound was prepared by a method similar to the method 1 of Example 20, using (2R)-2-(3,3-difluorocyclopentyl)-2-(4-fluorophenyl)-2-hydroxyacetic acid.

^{1}N-NMR ($CDCl_3$, δ ppm) : 1.39-1.55 (2H, m), 1.70-2.22 (10H, m), 2.73-2.81 (2H, m), 3.23-3.36 (1H, m), 3.43 (2H, s), 3.65-3.77 (1H, m), 4.43 (2H, brs), 6.31 (1H, d, J=7.6Hz), 6.37 (1H, d, J=8.2Hz), 6.67 (1H, d, J=7.4Hz), 7.01-7.08 (2H, m), 7.37 (1H, dd, J=7.4, 8.2Hz), 7.51-7.58 (2H, m)

low resolution FAB-MS (m/e, $(C_{24}H_{29}F_3N_4O_2 + H)^+$): 463.

Referential Example 1

(2R)-2 -[(1R)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one and (2R,5R)-2-(t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

[0204] To a mixture of 510 mg of (2R,5R)-2-(t-butyl)-5-phenyl-1,3-dioxolan-4-one which had been synthesized by the method of D. Seebach, et al. [Tetrahedron. Vol. 40, pp. 1313-1324 (1984)] in 20 ml of tetrahydrofuran and 1 ml of hexamethylphosphoric triamide, 1.7 ml of 1.5M lithium diisopropylamide solution in hexane was added dropwise at -78°C, followed by stirring for 30 minutes. Then a solution of 285 mg of cyclopentenone in 1.5 ml of tetrahydrofuran was added, and the reaction mixture was stirred for 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, resulting residue was purified by medium pressure silica gel column chromatography (developing solvent: hexane / ethyl acetate = 15/1 - 10/1). Thus 150 mg and 254 mg, respectively, of the title compounds were obtained as oil. Configuration of each of the compounds was determined from NOE of NMR.

Step 2. Synthesis of (2R)-2-[(1R)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetic acid

[0205] To a solution of 61 mg of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 3 ml of methanol, 1 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring for 3 hours at room temperature. Distilling the methanol off under reduced pressure, the residue was diluted with water and washed with diethyl ether. The aqueous layer was made acidic with 1N hydrochloric acid and extracted with diethyl ether. The organic layer was dried over anhydrous magnesium sulfate to provide 48 mg of the title compound.

Referential Example 2

(2R)-2-[(1S)-3-oxocyclopentyl]-2-hydroxy-2-phenylacetic acid

[0206] The title compound was prepared by a method similar to the step 2 of Referential Example 1, using (2R,5R) -2- (t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-3-dioxolan-4-one.

Referential Example 3

(2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

[0207] To a solution of 256 mg of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl)-5-phenyl-1,3-dioxolan-4-one in 3 ml of chloroform, 0.34 ml of diethylaminosulfur trifluoride was added under cooling with ice, followed by stirring for 20 hours at room temperature. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, resulting residue was pu-

rified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 20/1) to provide 115 mg of the title compound.

Step 2. Synthesis of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

[0208] The title compound was prepared by a method similar to the step 2 of Referential Example 1, using (2R,5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Referential Example 4

(2R)-2-[(1S)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

[0209] The title compound was prepared by a method similar to Referential Example 3, using (2R,5R)-2-(t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Referential Example 5

(2R)-2-[(1S)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1S)-3-hydroxycyclopentyl]-5-phenyl-1,3-dioxolan-4-one

[0210] To a solution of 169 mg of (2R,5R)-2-(t-butyl)-5-[(1S)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 2 ml of methanol, 71 mg of sodium borohydride was added under cooling with ice, followed by stirring for 30 minutes at the same temperature. The reaction mixture was diluted with diethyl ether, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 157 mg of the title compound was obtained as a colorless oil.

Step 2. Synthesis of (2R)-2-[(1S)-3-hydroxycyclopentyl]-2 -hydroxy-2-phenylacetic acid

[0211] The title compound was prepared by a method similar to the step 2 of Referential Example 1, using (2R,5R)-2-(t-butyl)-5-[(1S)-3-hydroxycyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Referential Example 6

(2R)-2-[(1R)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid

[0212] The title compound was prepared by a method similar to Referential Example 5, using (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Referential Example 7

(2R)-2-[(1S)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

[0213] The title compound was prepared by a method similar to Referential Example 3, using (2R)-2-[(1S)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid.

Referential Example 8

(2R)-2-[(1R)-3-fluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

[0214] The title compound was prepared by a method similar to Referential Example 3, using (2R)-2-[(1R)-3-hydroxycyclopentyl]-2-hydroxy-2-phenylacetic acid. Referential Example 9

2-cyclopentyl-2-hydroxy-2-phenylacetic acid

[0215] To a solution of 23.5 g of ethyl phenylglyoxylate in 200 ml of tetrahydrofuran, 70 ml of 2.0 M cyclopentylmagnesium chloride solution in diethyl ether was added dropwise under cooling with ice, followed by stirring for 30 minutes at the same temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammo-

nium chloride solution and brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 30/1 - 20/1) to provide 11 g of ethyl 2-cyclopentyl-2-hydroxy-2-phenylacetate, which was dissolved in 40 ml of methanol. To the solution 20 ml of 4N aqueous sodium hydroxide solution was added at room temperature, followed by stirring for 2 hours at the same temperature and further for 1 hour at 50°C. Distilling the methanol off under reduced pressure, the aqueous layer was made weakly acidic with 4N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and then brine and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was washed with 1 : 1 mixture of diethyl ether and hexane. Thus, 8.7 g of the title compound was obtained.

Referential Example 10

(2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R, 5R)-2-(t-butyl)-5-[(1R, 2R, 3S, 6R, 7S)-5-oxotricyclo[5. 2. 1. $0^{2.6}$]dec-8-en-3-yl]-5-phenyl-1,3-dioxolan-4-one

[0216] To a solution of 32 g of (2R,5R)-2-(t-butyl)-5-phenyl-1,3-dioxolan-4-one in 1.1 l of tetrahydrofuran, 105 ml of 1.5 M lithium diisopropylamide solution in hexane was added dropwise at -78°C, followed by stirring for 30 minutes, addition of 23. 4 g of (1S, 2R, 6R, 7R)-tricyclo[5.2.1.$0^{2, 6}$]dec-4,8-dien-3-one as dissolved in 300 ml of tetrahydrofuran, and further stirring for 1.5 hours. The reaction mixture was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride solution, water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was recrystallized from hexane-ethyl acetate. Thus 36.9 g of the title compound was obtained as a white solid.

Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1S)-4-oxo -2-cyclopentenyl]-5-phenyl-1,3-dioxolan-4-one

[0217] A solution of 25.6 g of the (2R,5R)-2-(t-butyl)-5-[(1R, 2R, 3S, 6R, 7S)-5-oxotricyclo-[5.2.1.$0^{2.6}$]-dec-8-en-3-yl]-5-phenyl-1,3-dioxolan-4-one as obtained in above step 1 in 350 ml of 1,2-dichlorobenzene was heated at 175°C for 7 hours with stirring, under nitrogen atmosphere. Thus precipitated solid was recovered by filtration and washed with hexane to provide 14 g of the title compound as a white solid.

Step 3. Synthesis of (2R.5R)-2-(t-butyl) -5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

[0218] To a solution of 19.1 g of the (2R, 5R)-2-(t-butyl)-5-[(1S)-4-oxo-2-cyclopentenyl]-5-phenyl-1,3-dioxolan-4-one as obtained in above step 2 in 700 ml of ethyl acetate, 2.0 g of 10% palladium-on-carbon was added, followed by stirring for 2 hours at ordinary temperature under hydrogen atmosphere. Filtering the catalyst off then distilling the solvent off under reduced pressure, the residue was recrystallized from hexane-ethyl acetate to provide 14 g of the title compound as a white solid.

Step 4. Synthesis of (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

[0219] The title compound was prepared by a method similar to Referential Example 3, using the (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1, 3-dioxolan-4-one as obtained in above step 3.

Referential Example 11

(2R)-2-(3,3-difluorocyclopentyl)-2-(4-fluorophenyl)-2-hydroxyacetic acid

[0220] The title compound was prepared by a method similar to the step 1 of Referential Example 1 and Referential Example 3, using (R)-4-fluoromandelic acid.

Referential Example 12

(2R)-2-(3,3-difluorocyclobutyl)-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R, 5R)-2-(t-butyl)-5-(3-benzyloxy-1-hydroxycyclobutyl)-5-phenyl-1,3-dioxolan-4-one

[0221] The title compound was prepared by a method similar to the step 1 of Referential Example 1, using 3-benzyloxycyclobutanone.

Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-(3-benzyloxycyclobutyl)-5-phenyl-1,3-dioxolan-4 -one

[0222] To a solution of 2.82 g of the (2R,5R)-2-(t-butyl)-5-(3-benzyloxy-1-hydroxycyclobutyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 1 in 80 ml of chloroform, 2.6 g of 4-dimethylaminopyridine was added under cooling with ice, followed by stirring for an hour at the same temperature. To the reaction mixture, 1 ml of methyl chloroglyoxylate was added, followed by stirring for an hour. The reaction mixture was diluted with chloroform, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was mixed with hexane / ethyl acetate = 1/1 liquid mixture and filtered through a silica gel column. Distilling the solvent of the filtrate off under reduced pressure, the residue was dissolved in 80 ml of toluene, and to the solution 56 mg of 2,2'-azobis(isobutyronitrile) and 2.3 ml of tri-n-butyltin hydride were added at room temperature, followed by heating for 4 hours at 110°C with stirring . Distilling the solvent off under reduced i pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 8/1) to provide 1.82 g of the title compound as an oily substance.

Step 3. Synthesis of (2R,5R)-2-(t-butyl)-5-(3-oxocyclobutyl)-5-phenyl-1,3-dioxolan-4-one

[0223] To a solution of 1.82 g of the (2R,5R)-2-(t-butyl)-5-(3-benzyloxycyclobutyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 2 in 40 ml of ethanol, 430 mg of palladium hydroxide-carbon was added, followed i by stirring for 6 hours at ordinary temperature under hydrogen atmosphere. The reaction mixture was filtered through Celite. Distilling the solvent off under reduced pressure, the residue was dissolved in 5 ml of dichloromethane, and the resulting solution was added dropwise at -78°C to a reaction mixture formed by adding 0.63 ml of oxalyl chloride to 1.1 ml of dimethylsulfoxide in 50 ml of dichloromethane at -78°C and stirring for 5 minutes. After stirring for 15 minutes at the same temperature, 0.5 ml of triethylamine was added to i the reaction mixture and stirred for 30 minutes while raising the temperature to room temperature. The reaction liquid was diluted with chloroform, washed with water and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, the residue was purified by silica gel column chromatography (developing solvent: hexane / ethyl acetate = 8/1) to provide 1.36 g of the title compound as an oily substance.

Step 4. Synthesis of (2R)-2-(3,3-difluorocyclobutyl)-2-hydroxy-2-phenylacetic acid

[0224] The title compound was prepared by a method similar to Referential Example 3, using the (2R,5R)-2-(t-butyl)-5-(3-oxocyclobutyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 3.

Referential Example 13

(2R)-2-(4,4-difluorocyclohexyl)-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-(1,4-dioxaspiro[4.5]-dec-8-yl)-5-phenyl-1,3-dioxolan-4-one

[0225] The title compound was prepared by a method similar to the steps 1 and 2 of Referential Example 12, using 1,4-dioxa-8-oxospiro[4.5]decane.

Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-(4-oxocyclohexyl)-5-phenyl-1,3-dioxolan-4-one

[0226] To a solution of 83 mg of the (2R,5R)-2-(t-butyl)-5-(1,4-dioxaspiro[4.5]dec-8-yl)-5-phenyl-1,3-dioxolan-4-one in a mixture of 4 ml of acetone and 0.4 ml of water, 52 mg of p-toluenesulfonic acid was added at room temperature, followed by stirring for 13 hours at 50°C. Distilling the acetone off under reduced pressure, the residue was diluted with ethyl acetate, washed with saturated aqueous sodium bicarbonate solution and then brine, and dried over anhydrous magnesium sulfate. Distilling the solvent off under reduced pressure, 70 mg of the title compound was obtained

as an oil.

Step 3. Synthesis of (2R)-2-(4,4-difluorocyclohexyl)-2-hydroxyphenylacetic acid

[0227] The title compound was prepared by a method similar to Referential Example 3, using the (2R,5R)-2-(t-butyl)-5-(4-oxocyclohexyl)-5-phenyl-1,3-dioxolan-4-one as obtained in above step 2.

Referential Example 14

(2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

Step 1. Synthesis of (2R,5R)-2-(t-butyl)-5-[[(1R)-3-hydroxyiminocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

[0228] To a solution of 46 mg of (2R,5R)-2-(t-butyl)-5-[(1R)-3-oxocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 1.5 ml of pyridine, 85 mg of hydroxylamine hydrochloride was added and the mixture was stirred for 1 hour at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine, and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 55 mg of the title compound.

Step 2. Synthesis of (2R,5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one

[0229] To a mixture of 20 mg of nitrosonium tetra-fluoro borate and 0.5 ml of 70% hydrogen fluoride-pyridine, a solution of 34 mg of (2R,5R)-2-(t-butyl)-5-[(1R)-3-hydroxyiminocyclopentyl]-5-phenyl-1,3-dioxolan-4-one in 0.5 ml of dichloromethane was added under ice-cooling. The mixture was stirred for 10 minutes at 0°C and 5 hours at room temperature. Water was added to the reaction mixture under ice-cooling and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and then brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give 35 mg of the title compound.

Step 3. (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid

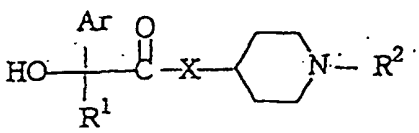
[0230] The title compound was prepared by a method similar to the step 2 of Referential Example 1, using (2R, 5R)-2-(t-butyl)-5-[(1R)-3,3-difluorocyclopentyl]-5-phenyl-1,3-dioxolan-4-one.

Industrially utilizability

[0231] The fluorine-containing 1,4-disubstituted piperidine derivatives of the present invention have selective antagonistic activity for muscarinic M_3 receptors, and exhibit excellent oral activity, duration of action and pharmacokinetics, so that they have little side effects and are safe and effective. Hence, they are very useful in the treatment or prophylaxis of diseases such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system: urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystisis: and motion sickness.

Claims

1. Novel fluorine-containing 1,4-disubstituted piperidine derivatives represented by the general formula [I]



[I]

and pharmaceutically acceptable salts thereof,

[wherein:

Ar represents a phenyl group which may be substituted with 1 to 3 substituents selected from the group, consisting of C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, amino and C_1-C_6 alkylamino;
R^1 is 3,3-difluorocyclopentyl; R^2 is 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl, 3-furylmethyl, 2-pyridylmethyl or benzyl (any 1-3 hydrogen atoms on the ring in the thienylmethyl, furylmethyl, pyridylmethyl or benzyl group may be substituted with C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, amino or C_1-C_6 alkylamino);
and
X stands for 0 or NH.

2. The compounds or their pharmaceutically acceptable salts according to Claim 1, in which the compounds represented by the general formula [I] is:

(2R)-N-[1-(6-methylpyridin-2-yl-methyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-thienylmethyl)piperidin-4-yl]-2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(2-furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(2-pyridylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-methoxybenzyl)piperidin-4-y1]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-(1-benzylpiperidin-4-yl)-2-[(1R)-3, 3-d ifluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(2-thienylmethyl)piperidin-4-yl]-2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(6-amino-4-methoxypyridin-2-ylmethyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-amino-5-methylbenzyl) piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(2-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
N-[1-(4-aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(4-amino-3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3,5-diaminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(5-methylfuran-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(4-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-amino-5-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(4-amino-3-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(6-amino-4-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-amino-4-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(5-amino-2-fluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(2-amino-4-chloropyridin-6-ylmethyl)-piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(3-amino-5-chlorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
(2R)-N-[1-(4-amino-3,5-difluorobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide
or
(2R) -N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-(4-fluorophenyl)-

2-hydroxyacetamide.

3. The compound according to claim 1 which is
(2R)-N-[1-(6-aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3, 3-difluorocyclopentyl]-2-hydroxy-2-phenylacetamide or a pharmaceutical acceptable salt thereof.

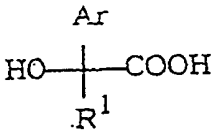
4. A pharmaceutical composition composed of a compound of the general formula [I] as presented in Claim 1 or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable adjuvant.

5. A pharmaceutical composition as defined in Claim 4 which is used for treatment or prophylaxis of diseases associated with muscarinic M_3 receptors, eg., such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system: urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystisis: and motion sickness.

6. Use of a compound of the general formula [I] as defined in Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament
for treatment or prophylaxis of diseases associated with muscarinic M_3 receptors, eg., such respiratory diseases as chronic obstructive pulmonary diseases, chronic bronchitis, asthma and rhinitis: digestive diseases such as irritable bowel syndrome, convulsive colitis, diverticulitis and pain accompanying contraction of smooth muscles of the digestive system: urinary disorders like urinary incontinence and frequency in neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystisis: and motion sickness.

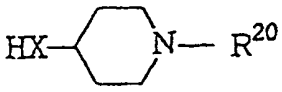
7. A process for preparation of a fluorine-containing 1,4-disubstituted piperidine derivative of the general formula [I] as presented in Claim 1 which comprises

(a) reacting a carboxylic acid of the general formula [III]



[III]

[wherein Ar and R' have the same signification as defined in Claim 1]
or a reactive derivative thereof with a compound of the general formula [IV]



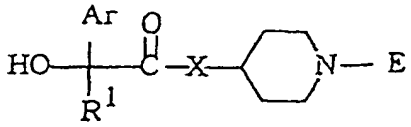
[IV]

[wherein R^{20} represents benzyl, 2-pyridylmethyl, 2-thienylmethyl, 3-thienylmethyl, 2-furylmethyl or 3-furylmethyl,
(any 1 to 3 hydrogen atoms on the ring may be substituted with C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, unprotected or protected amino, unprotected or protected C_1-C_6 alkylamino or aralkyloxycarbonyl;
protected amino or C_1-C_6 alkylamino group signifies amino or C_1-C_6 alkylamino group which is protected with benzyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl, trityl ; formyl, acetyl, propionyl, phenylacetyl, phenoxyacetyl, methoxycarbonyl, ethoxycarbonyl, isobutoxycarbonyl, t-butoxycarbonyl, 2-propenyloxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, trimethylsilyl and t-butyldimethylsilyl; and X stands for NH or 0]
or a salt thereof;
and when
R^{20} has protected amino or protected C_1-C_6 alkylamino group(s), removing the protective group(s); and when

R^{20} has C_1-C_7 alkoxycarbonyl or C_7-C_{10} aralkyloxycarbonyl, converting the same to amino; or
(b) reacting a carboxylic acid of the above general formula [III] or a reactive derivative thereof with a compound of the general formula [V]

[V]

[wherein E is a protective group for an imino group, which signifies similar protective groups to those for amino as above, and X is as defined above]
or a salt thereof; deprotecting the resulting compound of the general formula [VI]



[VI]

[wherein Ar and R' have the signification as defined in Claim 1 and X and E are as defined above]
thereafter reacting the same with a compound of the general formula [VII]

$$R^{20}\text{-}L \qquad [VII]$$

[wherein L represents halogen atoms such as chlorine, bromine and iodine; methanesulfonyloxy; or p-toluenesulfonyloxy; and R^{20} is as defined above]
if necessary in the presence of a base, and again if necessary conducting a conversion reaction of R^{20} similar to the above; or
(c) deprotecting a compound of the above general formula [VI] and subjecting it to a reductive alkylation reaction with a compound of the general formula [VIII]

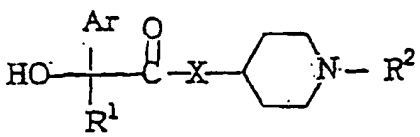
$$R^{21}\text{-}CHO \qquad [VIII]$$

[wherein R^{21} represents phenyl, 2-pyridyl, 2-thienyl, 3-thienyl, 2-furyl or 3-furyl (any 1 to 3 hydrogen atoms on the ring may be substituted with C_1-C_6 alkyl, trifluoromethyl, cyano, hydroxyl, nitro, C_1-C_7 alkoxycarbonyl, halogen, C_1-C_6 alkoxy, unprotected or protected amino, unprotected or protected C_1-C_6 alkylamino or aralkyloxycarbonyl); and protected amino and protected C_1-C_6 alkyl amine are as defined above], and if necessary conducting the conversion reaction of R^{21} similar to the above.

8. (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid.

Patentansprüche

1. Neue fluorenthaltende 1,4-disubstituierte Piperidinderivate, dargestellt durch die allgemeine Formel [I]:



[I]

und die pharmazeutisch annehmbaren Salze davon, worin:

Ar eine Phenylgruppe, die substituiert sein kann, mit 1 bis 3 Substituenten, ausgewählt aus der Gruppe, bestehend aus C_1-C_6-Alkyl, Trifluormethyl, Cyano, Hydroxyl, Nitro, C_1-C_7-Alkoxycarbonyl, Halogen, C_1-C_6-Alkoxy, Amino und C_1-C_6-Alkylamino, bedeutet;

R^1 3,3-Difluorcyclopentyl bedeutet;

R^2 2-Thienylmethyl, 3-Thienylmethyl, 2-Furylmethyl, 3-Furylmethyl, 2-Pyridylmethyl oder Benzyl (wobei 1 bis 3 Wasserstoffatome an dem Ring in der Thienylmethyl-, Furylmethyl-, Pyridylmethyl- oder Benzylgruppe mit C_1-C_6-Alkyl, Trifluormethyl, Cyano, Hydroxyl, Nitro, C_1-C_7-Alkoxycarbonyl, Halogen, C_1-C_6-Alkoxy, Amino oder C_1-C_6-Alkylamino substituiert sein kann bzw. können) bedeutet; und

X für 0 oder NH steht.

2. Verbindungen und ihre pharmazeutisch annehmbaren Salze nach Anspruch 1, wobei die Verbindungen, die durch die allgemeine Formel [I] dargestellt werden, sind:

(2R)-N-[1-(6-Methylpyridin-2-yl-methyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(2-Furylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(2-Pyridylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-(1-Benzylpiperidin-4-yl)-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Fluorbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Chlorbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(2-Thienylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(6-Amino-4-methoxypyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Amino-5-methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(2-Aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
N-[1-(4-Aminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(4-Amino-3-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3,5-Diaminobenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(5-Methylfuran-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Methylbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(4-Methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Amino-5-methoxybenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(4-Amino-3-fluorbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(6-Amino-4-methylpyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Amino-4-fluorbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(5-Amino-2-fluorbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(2-Amino-4-chlorpyridin-6-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(3-Amino-5-chlorbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid
(2R)-N-[1-(4-Amino-3,5-Difluorbenzyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid oder
(2R)-N-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-(4-fluorphenyl)-2-hy-

droxyacetamid.

3. Verbindung nach Anspruch 1, nämlich
(2R)-N-[1-(6-Aminopyridin-2-ylmethyl)piperidin-4-yl]-2-[(1R)-3,3-difluorcyclopentyl]-2-hydroxy-2-phenylacetamid oder ein pharmazeutisch annehmbares Salz davon.

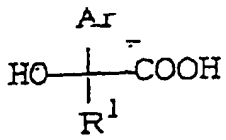
4. Pharmazeutische Zubereitung, zusammengesetzt aus einer Verbindung der allgemeinen Formel [I], wie in Anspruch 1 dargestellt, oder einem pharmazeutisch annehmbaren Salz davon und mindestens einem pharmazeutisch annehmbaren Adjuvans.

5. Pharmazeutische Zubereitung nach Anspruch 4, die für die Behandlung oder Prophylaxe von Krankheiten verwendet wird, die mit Muscarin-M_3-Rezeptoren assoziiert sind, beispielsweise Erkrankungen der Atemwege, wie chronische obstruktive Lungenkrankheiten, chronische Bronchitis, Asthma und Rhinitis: Krankheiten des Verdauungssystems, wie Reizdarmsyndrom, konvulsive Colitis, Divertikulitis und Schmerz, der mit der Kontraktion der glatten Muskeln des Verdauungssystems einhergeht: Harnwegserkrankungen, wie Urin-Inkontinenz und Häufigkeit an neurogener Pollakiurie, neurogene Blase, nächtliche Enuresis, schwache Blase, Blasenkrampf und chronische Cystitis: und Reisekrankheit.

6. Verwendung einer Verbindung der allgemeinen Formel [I], wie in Anspruch 1 definiert, oder eines pharmazeutisch annehmbaren Salzes davon für die Herstellung eines Arzneimittels für die Behandlung oder Prophylaxe von Krankheiten, die mit Muscarin-M_3-Rezeptoren assoziiert sind, beispielsweise Erkrankungen der Atemwege, wie chronische obstruktive Lungenkrankheiten, chronische Bronchitis, Asthma und Rhinitis: Krankheiten des Verdauungssystems, wie Reizdarmsyndrom, konvulsive Colitis, Divertikulitis und Schmerz, der mit der Kontraktion der glatten Muskeln des Verdauungssystems einhergeht: Harnwegserkrankungen, wie Urin-Inkontinenz und Häufigkeit an neurogener Pollakiurie, neurogene Blase, nächtliche Enuresis, schwache Blase, Blasenkrampf und chronische Cystitis: und Reisekrankheit.

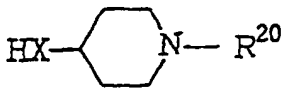
7. Verfahren zur Herstellung von fluorenthaltenden 1,4-disubstituierten Piperidinderivaten der allgemeinen Formel [I] nach Anspruch 1, umfassend:

(a) die Umsetzung einer Carbonsäure der allgemeinen Formel [III]



[III]

[worin Ar und R^1 die gleiche Bedeutung wie in Anspruch 1 gegeben besitzen] oder eines reaktiven Derivats davon mit einer Verbindung der allgemeinen Formel [IV]



[IV]

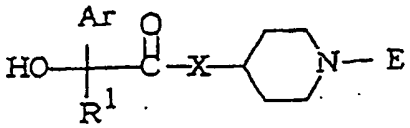
[worin R^{20} Benzyl, 2-Pyridylmethyl, 2-Thienylmethyl, 3-Thienylmethyl, 2-Furylmethyl oder 3-Furylmethyl bedeutet (wobei 1 bis 3 Wasserstoffatome am Ring substituiert sein können mit C_1-C_6-Alkyl, Trifluormethyl, Cyano, Hydroxyl, Nitro, C_1-C_7-Alkoxycarbonyl, Halogen, C_1-C_6-Alkoxy, ungeschütztem oder geschütztem Amino, ungeschütztem oder geschütztem C_1-C_6-Alkylamino oder Aralkyloxycarbonyl); wobei geschütztes Amino oder C_1-C_6-Alkylamino eine Amino- oder C_1-C_6-Alkylaminogruppe bedeutet, die mit Benzyl, p-Methoxybenzyl, p-Nitrobenzyl, Benzhydryl, Trityl; Formyl, Acetyl, Propionyl, Phenylacetyl, Phenoxyacetyl, Methoxycarbonyl, Ethoxycarbonyl, Isobutoxycarbonyl, t-Butoxycarbonyl, 2-Propenyloxycarbonyl, Benzyloxycarbonyl, p-Nitrobenzyloxycarbonyl, Trimethylsilyl oder t-Butyldimethylsilyl geschützt ist; und X NH oder 0 bedeutet] oder einem Salz davon; und wenn R^{20} eine oder mehrere geschützte Amino- oder geschützte C_1-C_6-Alkylaminogruppe/gruppen enthält, Entfernung der Schutzgruppe(n); und wenn R^{20} C_1-C_7-Alkoxycarbonyl oder C_7-C_{10}-Aralky-

loxycarbonyl enthält, Umwandlung davon zu Amino; oder

(b) Umsetzung einer Carbonsäure der obigen allgemeinen Formel [III] oder eines reaktiven Derivats davon mit einer Verbindung der allgemeinen Formel [V]

[V]

[worin E eine Schutzgruppe für eine Iminogruppe bedeutet, welche ähnliche Schutzgruppen bezeichnet, wie sie oben für die Aminogruppe aufgeführt wurden, und X die oben gegebene Definition besitzt]
oder einem Salz davon; Schutzgruppenabspaltung bei der entstehenden Verbindung der allgemeinen Formel [VI]



[VI]

[worin Ar und R^1 die in Anspruch 1 gegebene Bedeutung besitzen und X und E die oben gegebenen Definitionen besitzen],
danach Umsetzung dieser Verbindung mit einer Verbindung der allgemeinen Formel [VII]

$$R^{20}\text{-}L \qquad [VII]$$

[worin L Halogenatome, wie Chlor, Brom und Iod; Methansulfonyloxy; oder p-Toluolsulfonyloxy bedeutet; und R^{20} die oben gegebene Definition besitzt]
sofern erforderlich in Anwesenheit einer Base und erneut, sofern erforderlich, Durchführung einer Umwandlungsreaktion von R^{20}, ähnlich wie oben, oder

(c) Schutzgruppenabspaltung bei einer Verbindung der obigen allgemeinen Formel [VI] und Durchführung einer reduktiven Alkylierungsreaktion mit einer Verbindung der allgemeinen Formel [VIII]

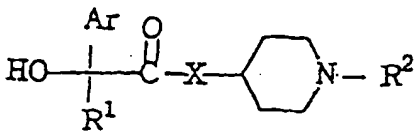
$$R^{21}\text{-}CHO \qquad [VIII]$$

[worin R^{21} Phenyl, 2-Pyridyl, 2-Thienyl, 3-Thienyl, 2-Furyl oder 3-Furyl bedeutet (wobei 1 bis 3 Wasserstoffatome am Ring substituiert sein können durch C_1-C_6-Alkyl, Trifluormethyl, Cyano, Hydroxyl, Nitro, C_1-C_7-Alkoxycarbonyl, Halogen, C_1-C_6-Alkoxy, ungeschütztes oder geschütztes Amino, ungeschütztes oder geschütztes C_1-C_6-Alkylamino oder Aralkyloxycarbonyl); und geschütztes Amino und geschütztes C_1-C_6-Alkylamino die oben gegebenen Bedeutungen besitzen]
und, sofern erforderlich, Durchführung einer Umwandlungsreaktion von R^{21}, ähnlich wie oben.

8. (2R)-2-[(1R)-3,3-Difluorcyclopentyl]-2-hydroxy-2-phenylessigsäure.

Revendications

1. Nouveaux dérivés fluorés de pipéridine disubstitués en 1,4, représentés par la formule générale [I]



[I]

et leurs sels pharmaceutiquement acceptables, formule dans laquelle :

Ar représente un groupe phényle qui peut être substitué par 1 à 3 substituants choisis dans la classe formée par les groupes alkyle en C_1-C_6, trifluorométhyle, cyano, hydroxyle, nitro, alcoxycarbonyle en C_1-C_7, halogéno, alcoxy en C_1-C_6, amine et alkylamino en C_1-C_6 ;
R^1 est un groupe 3,3-difluorocyclopentyle ;
R^2 est un groupe 2-thiénylméthyle, 3-thiénylméthyle, 2-furylméthyle, 3-furylméthyle, 2-pyridylméthyle ou benzyle (1 à 3 atomes d'hydrogène quelconques sur le noyau dans le groupe thiénylméthyle, furylméthyle, pyridylméthyle ou benzyle peuvent être substitués par des groupes alkyle en C_1-C_6, trifluorométhyle, cyano, hydroxyle, nitro, alcoxycarbonyle en C_1-C_7, halogéno, alcoxy en C_1-C_6, amino ou alkylamino en C_1-C_6) ; et
X représente O ou NH.

2. Composés ou leurs sels pharmaceutiquement acceptables selon la revendication 1, les composés représentés par la formule générale [I] étant les suivants :

(2R)-N-[1-(6-méthylpyridine-2-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-thiénylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-furylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(2-furylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-pyridylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-méthoxybenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-(1-benzylpipéridine-4-yl)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-fluorobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-chlorobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(2-thiénylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(6-aminopyridine-2-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-(1-(6-amino-4-méthoxypyridine-2-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-amine-5-méthylbenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-aminobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(2-aminobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
N-[1-(4-aminobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(4-amino-3-méthoxybenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3,5-diaminobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(5-méthylfuranne-2-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R) -N-[1-(3-méthylbenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(4-méthoxybenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-amino-5-méthoxybenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(4-amino-3-fluorobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(6-amino-4-méthylpyridine-2-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-amino-4-fluorobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(5-amino-2-fluorobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacé-

tamide
(2R)-N-[1-(2-amino-4-chloropyridine-6-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(3-amino-5-chlorobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide
(2R)-N-[1-(4-amino-3,5-difluorobenzyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide ou
(2R)-N-[1-(6-aminopyridiné-2-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-(4-fluorophényl)-2-hydroxyacétamide.

3. composé selon la revendication 1, qui est le (2R)-N-[1-(6-aminopyridine-2-ylméthyl)pipéridine-4-yl]-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétamide ou un de ses sels pharmaceutiquement acceptables.

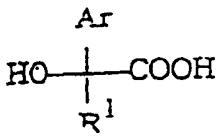
4. Composition pharmaceutique constituée d'un composé de formule générale [I] tel que défini dans la revendication 1 ou d'un de ses sels pharmaceutiquement acceptables et d'au moins un adjuvant pharmaceutiquement acceptable.

5. Composition pharmaceutique selon la revendication 4, qui est utilisée pour le traitement ou la prophylaxie de maladies associées aux récepteurs muscariniques M_3, par exemple des maladies respiratoires telles que des bronchopneumopathies chroniques obstructives, la bronchite chronique, l'asthme et la rhinite ; des maladies digestives telles que le syndrome du côlon irritable, la colite convulsive, la diverticulite et la douleur accompagnant une contraction des muscles lisses du système digestif ; des affections urinaires telles que l'incontinence et la fréquence urinaires dans la pollakiurie neurogène, la vessie neurogène, l'énurésie nocturne, la vessie instable, le cystospasme et la cystite chronique ; et le mal des transports.

6. Utilisation d'un composé de formule générale [I] tel que défini dans la revendication 1 ou d'un de ses sels pharmaceutiquement acceptables pour la fabrication d'un médicament destiné au traitement ou à la prophylaxie de maladies associées aux récepteurs muscariniques M_3, par exemple des maladies respiratoires telles que des bronchopneumopathies chroniques obstructives, la bronchite chronique, l'asthme et la rhinite ; des maladies digestives telles que le syndrome du côlon irritable, la colite convulsive, la diverticulite et la douleur accompagnant une contraction des muscles lisses du système digestif ; des affections urinaires telles que l'incontinence et la fréquence urinaires dans la pollakiurie neurogène, la vessie neurogène, l'énurésie nocturne, la vessie instable, le cystospasme et la cystite chronique ; et le mal des transports.

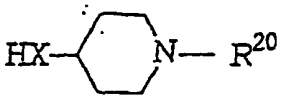
7. Procédé pour la préparation d'un dérivé fluoré de pipéridine disubstitué en 1,4 de formule générale [I] tel que défini dans la revendication 1, qui comprend

(a) la réaction d'un acide carboxylique de formule générale [III]



[III]

[dans laquelle Ar et R' sont tels que définis dans la revendication 1]
ou d'un dérivé réactif de celui-ci, avec un composé de formule générale [IV]



[IV]

[où R^{20} représente un groupe benzyle, 2-pyridylméthyle, 2-thiénylméthyle, 3-thiénylméthyle, 2-furylméthyle ou 3-furylméthyle (1 à 3 atomes d'hydrogène quelconques sur le noyau peuvent être substitués par des groupes alkyle en C_1-C_6, trifluorométhyle, cyano, hydroxyle, nitro, alcoxycarbonyle en C_1-C_7, halogéno, alcoxy

en C_1-C_6, amino protégé ou non protégé ou alkylamino en C_1-C_6 protégé ou non protégé ou aralkyloxycarbonyle ;

un groupe amino ou alkylamino en C_1-C_6 protégé désigne un groupe amino ou alkylamino en C_1-C_6 qui est protégé par des groupes benzyle, *p*-méthoxybenzyle, *p*-nitrobenzyle, benzhydryle, trityle, formyle, acétyle, propionyle, phénylacétyle, phénoxyacétyle, méthoxycarbonyle, éthoxycarbonyle, isobutoxycarbonyle, *t*-butoxycarbonyle, 2-propényloxycarbonyle, benzyloxycarbonyle, *p*-nitrobenzyloxycarbonyle, triméthylsilyle et *t*-butyldiméthylsilyle ;

et X représente NH ou O]

ou un sel de celui-ci ; et

lorsque R^{20} contient un ou plusieurs groupes amino protégé ou alkylamino en C_1-C_6 protégé, l'élimination du ou des groupes protecteurs ; et

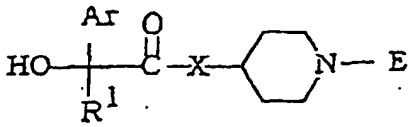
lorsque R^{20} contient un groupe alcoxycarbonyle en C_1-C_7 ou aralkyloxycarbonyle en C_7-C_{10}, la conversion de celui-ci en groupe amino ; ou

(b) la réaction d'un acide carboxylique de formule générale [III] ci-dessus ou d'un dérivé réactif de celui-ci avec un composé de formule générale [V]

[V]

[où E est un groupe protecteur pour un groupe imino, c'est-à-dire des groupes protecteurs similaires à ceux du groupe mentionnés pour le groupe amino ci-dessus, et X est tel que défini ci-dessus]

ou un sel de celui-ci ; la déprotection du composé résultant de formule générale [VI]



[VI]

[où Ar et R' sont tels que définis dans la revendication 1 et X et E sont tels que définis ci-dessus]

puis la réaction de celui-ci avec un composé de formule générale [VII]

$$R^{20}\text{-L} \qquad \text{[VII]}$$

[où L représente un atome d'halogène tel qu'un atome de chlore, brome ou iode, un groupe méthanesulfonyloxy ou un groupe *p*-toluènesulfonyloxy ; et

R^{20} est tel que défini ci-dessus]

si nécessaire en présence d'une base, et si nécessaire encore l'exécution d'une réaction de conversion de R^{20} similaire à celle indiquée ci-dessus ; ou

(c) la déprotection d'un composé de formule générale [VI] ci-dessus et l'exécution sur celui-ci d'une réaction d'alkylation réductive avec un composé de formule générale [VIII]

$$R^{21}\text{-CHO} \qquad \text{[VIII]}$$

[où R^{21} représente un groupe phényle, 2-pyridyle, 2-thiényle, 3-thiényle, 2-furyle ou 3-furyle (1 à 3 atomes d'hydrogène quelconques sur le noyau peuvent être substitués par des groupes alkyle en C_1-C_6, trifluorométhyle, cyano, hydroxyle, nitro, alcoxycarbonyle en C_1-C_7, halogéno, alcoxy en C_1-C_6, amino protégé ou non protégé, alkylamino en C_1-C_6 protégé

ou non protégé ou aralkyloxycarbonyle) ; et les groupes amino protégés et alklamino en C_1-C_6 protégés sont tels que définis ci-dessus],

et si nécessaire l'exécution de la réaction de conversion de R^{21} comme ci-dessus.

8. Acide (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phénylacétique.